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(71) *Sökande* *Astra AB, Södertälje SE*
Applicant (s)

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Evy Morin

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PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

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NEW 3-ARYL PROPIONIC ACID DERIVATIVES AND ANALOGS

Field of invention

The present invention releates to certain novel 3-aryl-2-hydroxypropionic acid derivatives and analogs, to a process for preparing such compounds, having the utility in clinical conditions associated with insulin resistance, to methods for their therapeutic use and to pharmaceutical compositions containing them.

Background of the invention

Insulin resistance, defined as reduced sensitivity to the actions of insulin in the whole body or individual tissues such as skeletal muscle, myocardium, fat and liver prevail in many individuals with or without diabetes mellitus. The insulin resistance syndrome, IRS, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinemia, possibly non insulin dependent diabetes mellitus (NIDDM), arterial hypertension, central (visceral) obesity, dyslipidemia observed as deranged lipoprotein levels typically characterized by elevated VLDL (very low density lipoproteins) and reduced HDL (high density lipoproteins) concentrations; and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In non-insulin dependent diabetes mellitus these atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is at present only limited awareness of the need to increase the insulin sensitivity in IRS and thus to correct the dyslipidemia which is considered to cause the accelerated progress of atherosclerosis.

Furthermore there is at present no pharmacotherapy available to adequately correct the metabolic derangements associated with IRS. To date, the treatment of NIDDM has been focused on correction of the deranged control of carbohydrate metabolism associated with the disease. Stimulation of endogenous insulin secretion by means of secretagogues, like sulphonylureas, and if necessary administration of exogenous insulin are methods frequently used to normalize blood sugar but that will, if anything, further enhance insulin resistance and will not correct the other manifestations of IRS nor reduce cardiovascular morbidity and mortality. In addition such treatment involves a significant risk of hypoglycemia with associated complications.

Other therapeutic strategies have focused on aberrations in glucose metabolism or absorption, including biguanides, such as methformin, or glucosidase inhibitors, such as acarbose. Although these agents have been efficacious to a degree, their limited clinical effect is associated with side effects.

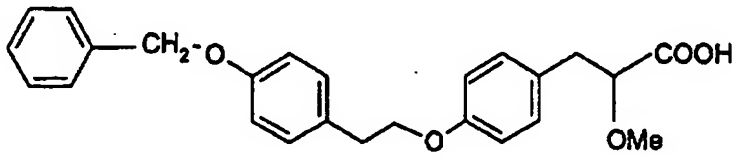
A novel therapeutic strategy involves the use of insulin sensitizing agents, such as the thiazolidinediones which at least in part mediate their effects via an agonistic action on nuclear receptors of the peroxisome proliferator activated receptor (PPAR) family. Ciglitazone is the prototype in this class. In animal models of IRS these compounds seem to correct insulin resistance and the associated hypertriglyceridaemia and hyperinsulinemia, as well as hyperglycemia in diabetes, by improving insulin sensitivity via an effect on lipid transport and handling, leading to enhanced insulin action in skeletal muscle, liver and adipose tissue.

Ciglitazone as well as later described thiazolidinediones in clinical development either have been discontinued reportedly due to unacceptable toxicity or show inadequate

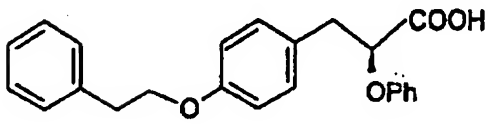
potency. Therefore there is a need for new and better compounds with insulin sensitizing properties.

Prior art

Compounds of the formula



and



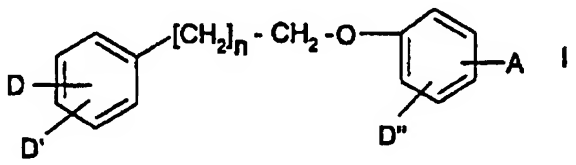
and certain derivatives thereof disclosed in US 5 306 726 and WO 91/19702 are said to be useful as hypoglycemic and hypocholesterolemic agents, and in US 5 232 945 said to be useful in the treatment of hypertension.

AU 650 429 discloses structurally related compounds, but claimed to have different properties: diuretic, antihypertensive, platelets anti-aggregating and anti-lipoxygenase properties.

EP 139 421 discloses compounds having the ability to lower blood lipid and blood sugar levels. Among these compounds is troglitazone, a compound that has reached the market for treatment of NIDDM or decreased glucose tolerance.

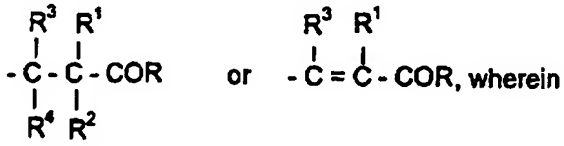
Description of the invention

The invention relates to compounds of the general formula (I)



and stereo and optical isomers and racemates thereof as well as pharmaceutically acceptable salts, solvates and hydrates thereof, in which formula

A is situated in the orto, meta or para position and represents



R is -OR^a, wherein R^a represents hydrogen, alkyl, aryl or alkylaryl;
-NR^bR^a, wherein R^b and R^a are the same or different and R^b represents hydrogen, alkyl, aryl, alkylaryl, cyano, - OH, -Oalkyl, -Oaryl, -Oalkylaryl, -COR^c or -SO_2R^d, wherein R^c represents hydrogen, alkyl, aryl or alkylaryl and R^d represents alkyl, aryl or alkylaryl;

R^1 is alkyl, aryl, alkylaryl, alkene, alkyne, cyano,
-OR^e, wherein R^e is alkyl, acyl, aryl or alkylaryl;
-$[CH_2]_m$ -OR^f, wherein R^f represents hydrogen, alkyl, acyl, aryl or alkylaryl and m represents an integer 1-8;
-O-$[CH_2]_m$ -OR^f, wherein m and R^f are as defined above;
-OSO_2R^d, wherein R^d is as defined above;

-OCONR^{a}R^c, wherein R^a and R^c are as defined above;

-SR^d, wherein R^d is as defined above;

-SO$_2$NR^{a}R^f, wherein R^f and R^a are as defined above;

-SO$_2$OR^a, wherein R^a is as defined above;

-SOR^d, wherein R^d is as defined above;

-SO$_2$R^d, wherein R^d is as defined above;

-NR^{a}R^g, wherein R^a is as defined above and R^g represents hydrogen, alkyl, aryl, alkylaryl or -SO$_2$R^d, wherein R^d is as defined above;

-NR^{c}COR^a, wherein R^c and R^a are as defined above;

-NR^{c}COOR^d, wherein R^c and R^d are as defined above;

-NR^{f}CONR^{a}R^c, wherein R^f, R^a and R^c are as defined above;

- COR^f, wherein R^f is as defined above;

- COOR^d, wherein R^d is as defined above; or

-CONR^{c}R^a, wherein R^c and R^a are as defined above;

R^2 is hydrogen, alkyl, aryl, or alkylaryl,

R^3 and R^4 are the same or different and each represents hydrogen, alkyl, aryl, alkylaryl or -OR^f, wherein R^f is as defined above;

n is an integer 1-6,

D is situated in the orto, meta or para position and represents

-OSO$_2$R^d, wherein R^d is as defined above;

-OCONR^{f}R^a, wherein R^f and R^a are as defined above;

-NR^{c}COOR^d, wherein R^c and R^d are as defined above;

-NR^{c}COR^a, wherein R^c and R^a are as defined above;

-NR^{g}R^a, wherein R^g and R^a are as defined above, provided that R^g and R^a are not simultaneously hydrogen;

-NR^{f}CONR^{a}R^c, wherein R^c, R^a and R^f are as defined above;

-SO$_2$R^d, wherein R^d is as defined above;

-SOR^d, wherein R^d is as defined above;

-SR^c, wherein R^c is as defined above;

-SO$_2$NR^{a}R^f, wherein R^f and R^a are as defined above;

$-SO_2OR^a$, wherein R^a is as defined above;

-CN,

$-CONR^cR^a$, wherein R^c and R^a are as defined above;

D' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

D'' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$ wherein R^f and R^b are as defined above;

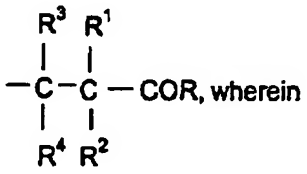
$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above.

The present invention does not comprise (S)- and (R)-2-ethoxy-3-[4-(2-{4-[methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid.

The compounds of the formula I are surprisingly effective in conditions associated with insulin resistance.

Category A2: preferred compounds of the present invention are those of formula I wherein A is situated in the meta or para position and represents,



R is $-OR^a$ wherein R^a is as defined above;

R^1 is alkyl, aryl, alkylaryl, alkene, alkyne, cyano,
$-OR^e$, wherein R^e is as defined above;
$-[CH_2]_m-OR^f$ wherein R^f and m are as defined above;
$-O-[CH_2]_m-OR^f$, wherein m and R^f are as defined above;
$-OCONR^aR^c$, wherein R^a and R^c are as defined above;
$-SR^d$, wherein R^d is as defined above;
$-NR^aR^g$, wherein R^a and R^g are as defined above;
$-COOR^d$, wherein R^d is as defined above;

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen, alkyl, aryl, alkylaryl or $-OR^f$, wherein R^f is as defined above;

n is an integer 1-3,

D is situated in the orto, meta or para position and represents
$-OSO_2R^d$, wherein R^d is as defined above;
$-OCONR^fR^a$, wherein R^f and R^a are as defined above;
$-NR^cCOOR^d$, wherein R^c and R^d are as defined above;
$-NR^cOR^a$, wherein R^c and R^a are as defined above;
$-NR^gR^a$, wherein R^g and R^a are as defined above, provided that R^g and R^a are not simultaneously hydrogen;
$-NR^fCONR^aR^c$, wherein R^c, R^a and R^f are as defined above;
$-SO_2R^d$, wherein R^d is as defined above;
$-SR^c$, wherein R^c is as defined above;
$-CONR^cR^a$, wherein R^c and R^a are as defined above;

D' is situated in the orto, meta or para position and represents
hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;
$-OR^f$, wherein R^f is as defined above;
$-OSO_2R^d$, wherein R^d is as defined above;

D'' is situated in the orto, meta or para position and represents

hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above.

Category A3: further preferred compounds of the present invention are those within category A2, wherein

A is situated in the para position,

R is $-OR^a$,

R^1 is - Oalkyl,

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen or alkyl,

n is an integer 1-3,

D is situated in the orto, meta or para position and represents $-NR^cCOOR^d$ or $-NR^cCOR^a$, wherein R^d, R^a and R^c are as defined above;

D' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

D'' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above.

Category A 4: further preferred compounds of the present invention are those within category A 3, wherein

R is -OH, -Oalkyl or -Oalkylaryl,

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

n is the integer 2,

D is situated in the para position, and represents - $NHCOOR^d$ or $NHCOR^a$, wherein R^d and R^a are as defined above;

D' is hydrogen and

D'' is hydrogen.

Category A 5: further preferred compounds of the present invention are those within category A 2, wherein

A is situated in the para position,

R is - OR^a,

R^1 is - Oalkyl,

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen or alkyl,

n is an integer 1-3,

D is situated in the orto, meta or para position and represents $-SO_2R^d$, wherein R^d and R^c are as defined above;

D' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

D'' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above.

Category A 6: further preferred compounds of the present invention are those within category A 5, wherein

R is -OH, -Oalkyl or -Oalkylaryl,
R^2 is hydrogen,
R^3 is hydrogen,
R^4 is hydrogen,
n is the integer 2,
D is situated in the para position.
D' is hydrogen and
D" is hydrogen.

Category A 7: further preferred compounds of the present invention are those within category A 2, wherein

A is situated in the para position,
R is $-OR^a$,
R^1 is -Oalkyl,
R^2 is hydrogen or alkyl,
R^3 is hydrogen or alkyl,
R^4 is hydrogen or alkyl,
n is an integer 1-3,
D is situated in the orto, meta or para position and represents
$-SR^c$, wherein R^c is as defined above;
D' is situated in the orto, meta or para position and represents
hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;
$-OR^f$, wherein R^f is as defined above;
$-OSO_2R^d$, wherein R^d is as defined above;
D" is situated in the orto, meta or para position and represents

hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above.

Category A 8: further preferred compounds of the present invention are those within category A 7, wherein

R is -OH, -Oalkyl or -Oalkylaryl,

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

n is the integer 2,

D is situated in the para position,

D' is hydrogen and

D" is hydrogen.

Category A 9: further preferred compounds of the present invention are those within category A 2, wherein

A is situated in the para position,

R is $-OR^a$,

R^1 is -Oalkyl,

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen or alkyl,

n is an integer 1-3,

D is situated in the orto, meta or para position and represents $-OCONR^fR^a$, wherein R^f and R^a are as defined above;

D' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

D" is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above,

$-OSO_2R^d$, wherein R^d is as defined above.

Category A 10: further preferred compounds of the present invention are those within category A 9, wherein

R is -OH, -Oalkyl or -Oalkylaryl,

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

n is the integer 2,

D is situated in the para position, and represents $-OCONHR^d$, wherein R^d is defined as above;

D' is hydrogen and

D" is hydrogen.

Category A 11: further preferred compounds of the present invention are those within category A 2, wherein

A is situated in the para position,

R is $-OR^a$,

R^1 is - Oalkyl,

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen or alkyl

n is an integer 1-3,

D is situated in the orto, meta or para position and represents

$-NR^aSO_2R^d$, wherein R^d and R^a are as defined above;

D' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

D" is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above,

$-OSO_2R^d$, wherein R^d is as defined above.

Category A 12: further preferred compounds of the present invention are those within category A 11, wherein

R is -OH, -Oalkyl or -Oalkylaryl,

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

n is the integer 2,

D is situated in the para position, and represents $-NHSO_2R^d$ wherein R^d is as defined above;

D' is hydrogen and

D" is hydrogen.

Category A 13: further preferred compounds of the present invention are those within category A 2, wherein

A is situated in the meta or para position,

R is $-OR^a$,

R^1 is -Oalkyl,

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen or alkyl,

n is an integer 1-3,

D is situated in the orto, meta or para position and represents

$-OSO_2R^d$, wherein R^d is defined as above;

D' is situated in the orto, meta or para position and represents

hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, CN, NO_2, NR^fR^b, wherein R^f and R^b are as defined above,

$-OR^f$, wherein R^f is as defined above,

$-OSO_2R^d$, wherein R^d is as defined above.

D" is situated in the orto, meta or para position and represents

hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above,

$-OR^f$, wherein R^f is as defined above,

$-OSO_2R^d$, wherein R^d is as defined above.

Category A 14: further preferred compounds of the present invention are those within category A 13, wherein

A is situated in the para position,

R is -OH, -Oalkyl, -Oalkylaryl,

n is the integer 2,

D is situated in the para position.

Category A 15: further preferred compounds of the present invention are those within category A 14, wherein

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

D is $-OSO_2$ alkyl,

D' is hydrogen and

D'' is hydrogen.

Category A 16: further preferred compounds of the present invention are

2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid,

3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid,

2-ethoxy-3-{4-[2-(4-methanesulfonylphenyl)ethoxy]phenyl}propanoic acid,

2-ethoxy-3-{4-[2-(4-methylsulfanylphenyl)ethoxy]phenyl}propanoic acid,

2-ethoxy-3-[4-(2-{4-isobutyrylaminophenyl}ethoxy)phenyl]propanoic acid,

3-{4-[2-(4-*tert*-butylcarbamoyloxyphenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester and
2-ethoxy-3-{4-[2-(4-methanesulfonylaminophenyl)ethoxy]phenyl}propanoic acid.

Category A 17: further preferred compounds of the present invention are compounds which is one of the possible enantiomers.

In the present specification the expression "pharmaceutically acceptable salts" is intended to define but is not limited to such base salts as the alkali metal salts, alkaline earth metal salts, aluminium, zinc and bismuth salts, ammonium salts, salts with basic amino acids, and salts with organic amines.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates. Isomers may be separated using conventional techniques, e.g.

chromatography or fractional crystallization. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallization or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric esters by conventional means (e.g. HPLC, chromatography over silica) or by asymmetric synthesis. All stereoisomers are included within the scope of the invention.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes a straight or branched, substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

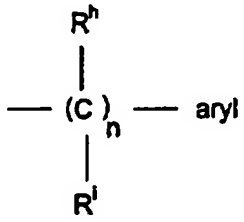
Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

Unless otherwise stated or indicated, the term "aryl" denotes a substituted or unsubstituted phenyl, furyl, thienyl or pyridyl group, or a fused ring system of any of these groups, such as naphthyl.

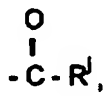
Unless otherwise stated or indicated, the term "substituted " denotes an alkyl or an aryl group as defined above which is substituted by one or more alkyl, alkoxy, halogen, amino, thiol, nitro, hydroxy, acyl, aryl or cyano groups.

Unless otherwise stated or indicated, the term "alkylaryl" denotes a



wherein n is an integer 1 to 6 and R^h and R^i are the same or different and each represents hydrogen or an alkyl or aryl group as defined above.

Unless otherwise stated or indicated, the term "acyl" denotes a group



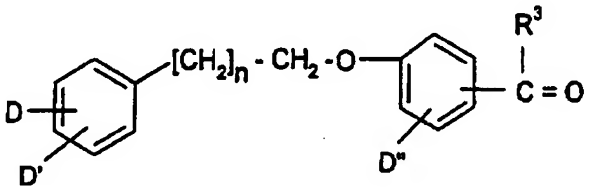
wherein R^j is hydrogen, alkyl, alkoxy, aryl and alkylaryl as defined above.

Unless otherwise stated or indicated the term "protective group" (R^p) denotes a protecting group as described in the standard text "Protecting groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts. The protective group may also be a polymer resin such as a Wang resin or a 2-chlorotrityl chloride resin.

Methods of preparation

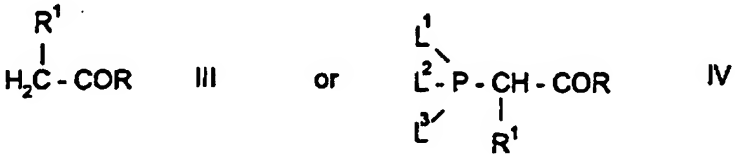
The compounds of the invention may be prepared as outlined below according to any of methods A-I. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

A. The compounds of the invention of formula I wherein R^2 and R^4 are hydrogen can be prepared by a condensation reaction, such as a Knoevenagel or Wittig type reaction, of a carbonyl compound of the formula II



II

with a compound of the formula III or IV



in which formulas D, D', D'', n, R, R^1 and R^3 are as defined above, and $L^1 = L^2 = L^3$ are phenyl or $L^1 = L^2$ are OR^d (wherein R^d is as defined above) and L^3 is =O, and if desired, followed by reduction of the obtained double bond and removal of protective groups.

A1. In the condensation step approximately equimolar amounts of reactants are heated in the presence of a mild base, such as sodium acetate or piperidine acetate to provide the olefin compound of formula I wherein A is the unsaturated moiety. This step may be carried out in the presence of a reaction inert solvent or in the absence of solvent at a temperature which is sufficiently high to cause at least partial melting of the reaction mixture. A preferred such temperature is in the range of 100°C to 250°C.

In a typical such reaction the aldehyde or ketone starting material and the compound of formula III are combined in approximately equimolar amounts with molar excess, pref. 1-5

fold molar excess, of anhydrous sodium acetate and the mixture is heated, at a temperature high enough to effect melting and if necessary under vacuum. The olefin compound of formula I wherein A is the unsaturated moiety, can then be isolated by mixing with water or acetone and followed by filtration of the precipitate, to obtain the crude product which is purified if desired, e.g. by recrystallization or by standard chromatographic methods.

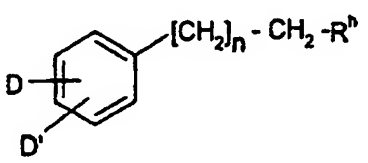
This reaction also takes place conveniently in a solvent such as toluene in presence of piperidine acetate. The reaction mixture is refluxed with water separation in a Dean-Stark apparatus. The solution is then cooled and the olefin product isolated and purified, by standard methods.

A2. The reaction can also be performed in the presence of titanium (IV) chloride and pyridine in a reaction inert solvent, such as chloroform.

A3. The condensation step could also be performed as a Wittig-type reaction (cf. Comprehensive Organic Synthesis vol. 1 p. 755-781 Pergamon Press) or as described in the experimental part.

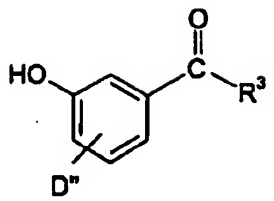
Approximately equimolar amounts of reactants II and IV, 1-2 equivalents of either, are stirred in the presence of a base such as trimethylguanidine or potassium carbonate in a 1-5 fold molar excess. This step may be carried out in the presence of a reaction inert solvent such as dichloromethane or isopropanol and at a suitable temperature (-10°C - + 60°C) and at a time long enough.

The compound of the formula II is prepared by coupling a compound of the formula V



V

with a compound of the formula VI



VI

at, for example alkylation conditions or by a Mitsunobu reaction (Tsunoda, Tetr. Lett. 34, 1639-42 (1993), when necessary followed by modifications of the D-groups as described in the experimental section.

The group R^h can be - OH or a leaving group, such as halogen or a alkylsulfonate, arylsulfonate or a triflate.

The alkylation reaction and the Mitsunobu reaction can be carried out as described below.

The compound of formula V can be prepared by standard procedures know to anyone skilled in the art, from commercial available starting materials or as described in the experimental section.

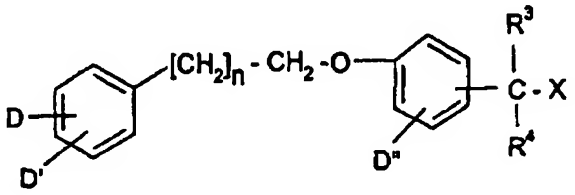
The reduction of the olefin may be carried out by employing a wide variety of reducing agents which are known to reduce carbon-carbon double bonds, such as catalytic hydrogenation in the presence of an appropriate catalyst, magnesium or sodium amalgam in a lower alcohol such as methanol, or hydrogen transfer reagents such as diethyl-2,5-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

The catalytic hydrogenation can be conducted in alcohol, cellosolves, protic polar organic solvents, ethers, alkoxyalkanes, lower alifatic acids, and particularly methanol, ethanol, methoxyethanol, dimethylformamide, tetrahydrofurane, dioxane, dimetoxyethane,

ethylacetate or acetic acid, preferably used alone or in mixture. Examples of the catalyst used include palladium black, palladium on carbon and platinum oxide. This reaction can proceed at normal temperature under normal pressure or at elevated temperature under increased pressure depending on the reactivity of the aimed reaction.

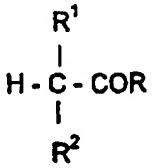
In case of hydrogen transfer reaction with diethyl-2,5-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate the reaction is conducted by mixing equimolar amounts of reactants and warming the mixture to melting (140°C - 250°C) under inert atmosphere or under vacuum.

B. The compounds of the invention of formula I where $A=CR^3R^4\text{-}CR^1R^2\text{-}COR$, can be prepared by an alkylation reaction with a compound of formula



VII

where in X is a leaving group such as halogen, alkylsulfonates, arylsulfonates or triflates, on a compound of formula VIII,

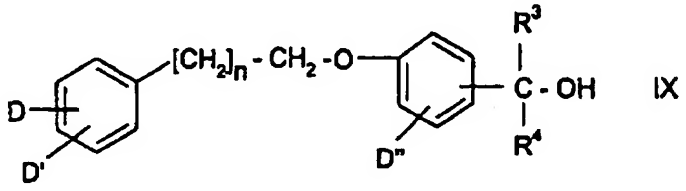


VIII

in which formulas D, D', D", n, R, R', R^3 are as defined above, R^2 is hydrogen, alkyl, aryl, or alkylaryl and R^4 is hydrogen, alkyl, aryl, alkylaryl or DR^f wherein R^f is as defined above, and if desired followed by removal of protective groups.

In the alkyation step the compound of formula VII is reacted with a compound of formula VIII in the presence of one or more bases such as potassium carbonate, triethylbenzylammonium chloride, sodium hydride, LDA, butyllithium or LHMDS (lithiumhexamethyldisilyl amine) and a reaction inert solvent such as acetonitrile, DMF or dichloromethane at a suitable temperature and time. The reaction can be carried out as described in the examples or by standard methods known in the litterature. (Synth. Comm. 19(788) 1167-1175 (1989)).

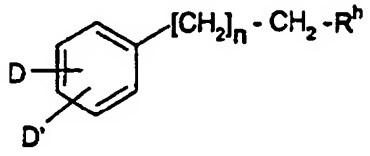
The compound of formula VII can be prepared from an alcohol of formula IX



IX

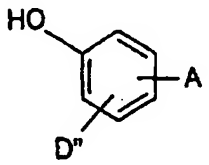
using standard methods or as described in the examples. The compound of formula IX can be prepared by reduction of a compound of formula II by standard methods or as described in the experimental section.

C. The compounds of the invention of formula I can be prepared by reaction of a compound of the formula



V

with a compound of the formula X



X

in which formulas D, D', D'' and n are as defined above, A represents $-CR^3R^4-CR^1R^2-COR$ or $-CR^3=CR^1-COR$, wherein R, R^1, R^2, R^3 and R^4 are as defined above and R^h is -OH or a leaving group such as halogen, alkylsulfonate, arylsulfonate, triflate, either by an alkylation reaction or a Mitsunobu reaction, when nessecary followed by deprotection of a protective group and modifications of the D-groups.

C1. In an alkylation reaction the leaving group R^h can be a sulfonate such as mesylate, nosylate, tosylate, or a halogen, such as bromine or iodine. The compounds of formula V and X, in approximately equimolar amounts or with an excess of either compound, are heated to reflux temperature in an inert solvent, such as isopropanol or acetonitrile, in the presence of a base, such as potassium carbonate or cesium carbonate.

The mixture is refluxed for the necessary time, typically between 0.5 h to 24 h, the work up procedure usually include filtration, for removal of solid salt, evaporation and extraction with water and an organic solvent such as dichloromethane, ethyl acetate, or diethyl ether. The crude product is purified if desired e.g. by recrystallization or by standard chromatographic methods.

C2. The Mitsunobu reaction can be carried out according to standard methods.

In a typical Mitzunobu reaction a compound of formula V, wherein the group R^h is a hydroxyl group, and a compound of formula X are mixed, in approximately equimolar amounts or with an excess of either compound, in an inert solvent, such as chloroform, dichloromethane, or tetrahydrofuran in approximately equimolar amounts. A slight molar

excess, 1-4 eqvivalents, of an azodicarboxylate, such as DEAD (diethyl azodicarboxylate) or ADDP (azodicarbonyl dipiperidine) and a phosphine (1-4 equivalents), such as tributylphosphine or triphenylphosphine are added and the reaction is stirred at a temperature high enough - for example room temperature - and a time long enough (1-24 hours) to obtain the crude product, which can be worked up according to standard litterature methods and if desired purified, e.g. by standard chromatographic methods.

D. The compounds of the invention of formula I wherein A is $-CR^3R^4-CR^1R^2-COR$ wherein R, R^2, R^3 and R^4 are as defined above and R^1 is

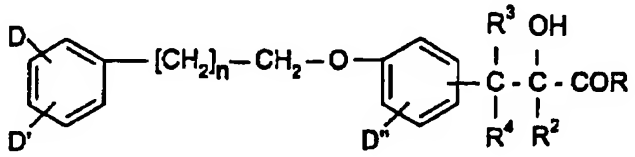
$-OR^e$ wherein R^e is as defined above,

$-O-[CH_2]_m-OR^f$, wherein m and R^f are as defined above,

$-OSO_2R^d$, wherein R^d is as defined above,

$-OCONR^aR^c$, wherein R^a and R^c are as defined above,

can be prepared by converting a compound of formula XI



XI

wherein D, D', D'', n, R, R^2, R^3 and R^4 are as defined above.

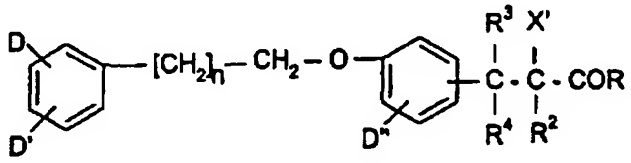
The reaction may be carried out as an alkylating reaction, a Mitsunobu reaction or an esterfication reaction. The alkylating reaction may be carried out using a variety of alcylating agents, such as ethyl halide. The esterfication reaction may be carried out using a variety of acylating and sulfonylating agents such as $Cl-CO-R^d$ and $Cl-SO_2-R^d$ (wherein R^d is as defined above).

The Mitsunobu reaction may be carried out as described above using an alcohol such as phenol, and the other reactions can be carried out in accordance with methods known to those skilled in the art or as described in the examples.

E. The compounds of the formula I wherein A is $-CR^3R^4-CR^1R^2-COR$, wherein R, R^2, R^3 and R^4 are as defined above and R^1 is

- OR^d, wherein R^d is as defined above,
- $O-[CH_2]_m-OR^f$, wherein R^f and m are as defined above,
- $-SR^d$, wherein R^d is as defined above,
- $-NR^aR^g$, wherein R^a and R^g are as defined above,
- $-NR^cCOR^d$, wherein R^c and R^d are as defined above,

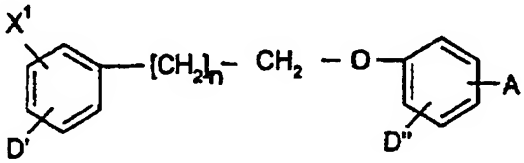
can be prepared by reacting a compound of the formula XII



XII

wherein D, D', D'', n, R, R^2, R^3, R^4 are as defined above and X' is halogen, with an amine, an alcohol or a thiol in a substitution reaction. The reaction can be carried out in accordance to methods known to those skilled in the art or as described in the examples.

F. The compounds of the invention of formula I wherein D is $-OSO_2R^d$, $-SR^c$, $-OCONR^fR^a$, $-NR^cCOOR^d$, $-NR^cCOR^a$, $-NR^gR^a$, $NR^fCONR^aR^c$ wherein R^a, R^c, R^d, R^f and R^g are as defined above, can be prepared by reacting a compound of formula XIII



XIII

wherein D', D'', n and A are as defined in method C and X^1 = -OH, -SH or $-NH_2$, with a suitable reagent, such as a sulfonylhalide, isocyanate, acylhalide, chloroformate, anhydride, alkylhalide and arylhalide, R^aOCOCl, R^dNCO, R^aCOX', $(Me_3COCO)_2O$, R^dSO_2X', R^dX',

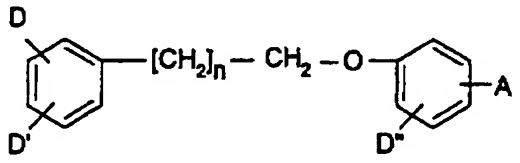
wherein R^d and R^a are as defined above and X' is halogen, when necessary in the presence of a base, such as triethylamine or pyridine and in an inert solvent such as dichloromethane or toluene eventually followed by removal of protective groups.

The reaction can be carried out in accordance with methods know to those skilled in the art or as described in the examples.

G. The compounds of the invention of formula I where R is OH can be prepared from a compound of formula I where in R is OR^P, wherein R^P is a protective group such as alkyl or a polymer resin such as Wang resin or 2-chlorotrityl chloride resin, by removal of the protective group by hydrolysis. The hydrolysis can be performed according to standard methods either under basic or acidic conditions.

H. The compound of the invention of formula I wherein R is NR^bR^a can be prepared by reacting a compound of formula I when R is OH with a compound of formula HNR^bR^a for example in the presence of a peptide coupling system (e.g. EDC, DCC, HBTU, TBTU or PyBop or oxalylchloride in DMF), an appropriate base (e.g. pyridine, DMAP, TEA or DiPEA) and a suitable organic solvent (e.g. dichloromethane, acetonitrile or DMF) in accordance to methods known to those skilled in the art or as described in the examples.

I. The compounds of the invention of formula I where $D=SO_2R^d$ or SOR^d, can be prepared by oxidizing a compound of formula XIV



XIV

wherein D', D'', n and A are as defined in method C and D is - SOR^d or -SR^d with an oxidizing agent such as m-chloroperoxybenzoic acid in an inert solvent such as dichloromethane eventually followed by removal of protective groups.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

In any of the preceeding methods of preparation A-I, where necessary, hydroxy, amino or other reactive groups may be protected using a protecting group, R^P as described in the standard text "Protective groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts. The protecting group R^P may also be a resin, such as Wang resin or 2-chlorotrityl chloride resin. The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore. Protecting groups may be removed in accordance to techniques which are well known to those skilled in the art.

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner wich adversely affects the yield of the desired product.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in

the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutical acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

The compounds of the invention may also be combined with other therapeutic agents which are useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidemias, dyslipidemias, diabetes and obesity.

Suitable daily doses of the compounds of the invention in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight, preferably 0.001-10 mg/kg body weight.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The present compounds of formula (I) will be adapted for treatment of clinical conditions associated with reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders. These clinical conditions will include, but will not be limited to, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, non insulin dependent diabetes mellitus (NIDDM) and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile of phenotype B, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoproteins (VLDL) triglycerides, low high density lipoproteins (HDL) cholesterol and the presence of small, dense, low density lipoproteins (LDL). Treatment

with the present compounds is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis. These cardiovascular disease conditions include macro-angiophaties causing myocardial infarction, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of their insulin sensitizing effect compounds of formula (1) are also expected to reduce the progress of clinical conditions associated with chronic hyperglycaemia in diabetes like the micro-angiophaties causing renal disease and retinal damage. Furthermore the compounds may be useful in treatment of various conditions outside the cardiovascular system associated with insulin resistance like the polycystic ovarian syndrome, as well as other diseases where PPAR activation is of benefit.

Working examples

^{1}H NMR and ^{13}C NMR measurements were performed on a BRUKER ACP 300 and Varian UNITY plus 400, 500 and 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ^{13}C frequencies of 75.5, 100.6, 125.7 and 150 MHz, respectively.

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Example 1. 2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid ethyl ester

(a) 2-(4-Methanesulfonyloxyphenyl)ethylmethanesulfonate

p-Hydroxyphenethyl alcohole (15 g; 0.108 mole) was dissolved in dichloromethane. Triethylamine (27.3 g; 0.27 mole) was added followed by addition of a solution of methanesulphonyl chloride (27.2 g; 0.239 mole) in dichloromethane at 0° C. The reaction was allowed to reach room temperature, then stirred at room temperature and followed by

TLC. The reaction mixture was filtered and the filtrate was washed with water. The solution was dried with sodium sulfate and then evaporated *in vacuo* to give 28 g (yield 88%) of 2-(4-methanesulfonyloxyphenyl)ethylmethanesulfonate.

(b) 4-[2-(4-Formylphenoxy)ethyl]phenylmethanesulfonate

2-(4-Methanesulfonyloxyphenyl)ethylmethanesulfonate (30 g; 0.102 mole) was dissolved in acetonitrile and slowly added to a mixture of p-hydroxybenzaldehyde (31.1 g; 0.255 mole) and potassium carbonate (41.46 g; 0.3 mole) in acetonitrile and refluxed until 2-(4-methanesulfonyloxyphenyl)ethylmethanesulfonate was consumed. The salts were filtered off, the solvent evaporated *in vacuo*, dichloromethane was added and the organic phase was washed with water. After evaporation of the solvent, purification by chromatography on silica gel using dichloromethane as eluent gave 21.6 g (yield 66 %) of 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate.

(c) 2-Ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester

Tetramethylguanidine (1.73 g; 15.0 mmole) was slowly added to a solution of 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate (4.49 g; 14.0 mmole) and ethoxy ethoxycarbonylmethyl-triphenylphosphonium chloride (5.62 g; 13.1 mmole) in chloroform (50 ml) at 0° C. After stirring at room temperature over night the solvent was evaporated *in vacuo*. When diethyl ether was added to the residue, triphenylphosphineoxide crystallized as white crystalls which were filtered off. The filtrate was evaporated *in vacuo*. The residue was purified by chromatography on silica gel using ethyl acetate in heptan (gradient 1.25-100 %) as eluents. The crude product crystallized upon standing. Recrystallization gave 2.18 g (yield 35 %) white crystalls of 2-ethoxy-3-{4-[2-(4-methanesulfonyloxy-phenyl)ethoxy]phenyl}acrylic acid ethyl ester.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.34-1.38 (2t, 2x6H, J=7 Hz for both), 3.11 (t, 2H, J=6 Hz), 3.13 (s, 3H), 3.98 (q, 2H, J=7 Hz), 4. 2 (t, 2H, J=6.8 Hz), 4.28 (q, 2H, J=7), 6.87 (dm, 2H,

J=9, unresolved), 6.95 (s, 1H), 7.23 (dm, 2H, J=9, unresolved), 7.33 (dm, 2H, J=9, unresolved), 7,73 (dm, 2H, J=9, unresolved).
^{13}C-NMR (125 MHz; $CDCl_3$): δ 14.3, 15.5, 35.0, 37.3, 61.0, 67.5, 68.1, 114.4, 122.0, 123.8, 126.6, 130.5, 131.7, 137.7, 143.1, 147.9, 159.0, 164.9.

(d) 2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid ethyl ester

2-Ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester (1.47 g; 3.38 mmole) was hydrogenated for 3 hours at atmospheric pressure in ethyl acetate (50 ml) using Pd/C (0.74 g, 5 %) as catalyst. The reaction mixture was filtered through celite and dried (magnesium sulfate), the solvent was evaporated *in vacuo* to give 1.44 g (yield 98 %) of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl]propanoic acid ethyl ester.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.16 (t, 3H, J=7 Hz), 1.23 (t, 3H, J=7 Hz), 2.92-2.96 (m, 2H), 3.09 (t, 2H, J=6.6), 3.13 (s, 3H), 3.31-3.38 (m, 1H), 3.56-3.63 (m, 1H), 3.94-3.98 (m, 1H), 4.12-4.19 (m, 4H), 6.8 (dm, 2H, J=8.8 Hz, unresolved), 7.14 (dm, 2H, J=8.9 Hz, unresolved), 7.22 (dm, 2H, J=8.9 Hz, unresolved), 7.33 (dm, 2H, J=8.6 Hz, unresolved).
^{13}C-NMR (125 MHz; $CDCl_3$): δ 14.2, 15.0, 35.1, 37.2, 38.4, 60.7, 66.1, 68.1, 80.3, 114.3, 121.9, 129.5, 130.4, 130.5, 138.0, 147.8, 157.4, 172.5.

Example 2. 2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid

Lithium hydroxide hydrate (0.12 g; 2.82 mmole) dissolved in water (10 ml) was slowly added to a solution of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)-phenyl]propanoic acid ethyl ester (1.12 g; 2.56 mmole) in tetrahydrofuran (30 ml). After stirring at room temperature for 3 hours water (50 ml) was added and tetrahydrofuran was removed by evaporation *in vacuo*. The water residue was acidified with hydrochloric acid

(2M), and the product was extracted three times with ethyl acetate, dried (magnesium sulfate), filtered and the solvent was evaporated *in vacuo* to give 1 g (yield 96 %) of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 2.91-2.99 (m, 1H), 3.03-3.11 (m, 3H), 3.12 (s, 3H), 3.39-3.47 (m, 1H), 3.57-3.64 (m, 1H), 4.01-4.06 (m, 1H), 4.14 (t, 2H, J=6.7 Hz), 6.81 (dm, 2H, J=8.6 Hz, unresolved), 7.15 (dm, 2H, J=8.6 Hz, unresolved), 7.22 (dm, 2H, J=8.6 Hz, unresolved), 7.33 (dm, 2H, J=8.6 Hz, unresolved).
^{13}C-NMR (125 MHz; $CDCl_3$): δ 15.0, 35.1, 37.2, 37.8, 66.8, 68.1, 79.7, 114.4, 121.9, 128.8, 130.49, 130.52, 137.9, 147.8, 157.5, 169.1.

Example 3. *N*-cyano-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic amide

DCC (0.444 g; 2.15 mmole) and N-hydroxy-succinimide (0.247 g; 2.15 mmole) were added to a solution of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl]propanoic acid (0.8 g; 1.96 mmole) in acetonitrile (20 ml) at 0° C. After stirring at room temperature over night a residue was filtered off and diisopropylethylamine (1 ml; 5.88 mmole) and cyanamide (0.165 g; 3.92 mmole) were added. After stirring over night the reaction mixture was poured onto potassium hydrogen sulfate (1M, 20 ml) and the crude product was extracted with ethyl acetate, washed with water and dried (sodium sulfate). The crude product was purified by chromatography on silica gel using ethyl acetate:heptane.acetic acid (10:10:1) as eluents to give 0.755 g (yield 89 %) of *N*-cyano-2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl]propanoic amide.

^{1}H NMR (500 MHz; CD_3OD): δ 7.39 (d, J=8.7 Hz, 2H), 7.25 (d, J=8.7 Hz, 2H), 7.14 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.6 Hz, 2H), 4.16 (t, J=6.6 Hz, 2H), 3.79 (dd, J=8.6 and 4.5 Hz, 1H), 3.53 (m,1H), 3.22 (m,1H), 3.17 (s, 3H), 3.07 (t, J=6.6 Hz, 2H), 2.86 (dd, J=13.9 and 4.5 Hz, 1H), 2.75 (dd, J=13.9 and 8.6 Hz, 1H), 1.07 (t, J=7.0 Hz, 3H).

Example 4. *N*-benzyloxy-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic amide

DCC (1 g; 4.85 mmole) and N-hydroxy-succinimide acid (0.56 g; 4.85 mmole) were added to a solution of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}-ethoxy)phenyl]propanoic (1.65 g; 4.04 mmole) in acetonitrile (25 ml) at 0° C. After 1 hour a residue was filtered off and diisopropylethylamine (1.82 g; 14.1 mmole) and benzyl hydroxylamine (1.24 g; 8.08 mmole) dissolved in acetonitrile were added. After stirring over night hydrochloric acid (2M) was added, the mixture was extracted with diethyl ether, washed with sodium carbonate solution and dried (magnesium sulfate). The crude product was purified by chromatography on silica gel using ethyl acetate:heptane (gradient 10-100 % ethyl acetate) as eluents to give 1.36 g (yield 66 %) of *N*-benzyloxy-2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl]propanoic amide.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.01(t, 3H, J=7.1 Hz), 2.82-2.90 (m, 1H), 3.03-3.11 (m, 3H), 3.12 (s, 3H), 3.36 (q, 2H, J=7.1 Hz), 3.91-3.96 (m, 1H), 4.13 (t, 2H, J=6.8 Hz), 4.76 (d, 1H, J=11.4 Hz), 4.88 (d, 1H, J=11.4 Hz) 6.79 (dm, 2H, J=8.8 Hz, unresolved), 7.12 (dm, 2H, J=8.8 Hz, unresolved), 7.21 (dm, 2H, J=8.8 Hz, unresolved), 7.27-7.36 (m, 7H), 8.69 (s, 1NH).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 15.0, 35.1, 37.3, 37.8, 66.7, 68.2, 78.3, 81.0, 114.2, 121.9, 128.5, 128.8, 129.17, 129.23, 130.5, 130.8, 135.0, 138.0, 147.8, 157.5, 168.8.

Example 5. 2-Ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic amide

Ammonia (g) was bubbled through a mixture of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid (2.9 g; 7.1 mmole) and benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (3.7 g; 7.1 mmole) in DMF (30 ml) for 3 hours at room temperature. Water and ethyl acetate were

added. The phases were seperated, the organic phase was washed with water, dried (magnesium sulfate) and the solvent was evaporated *in vacuo*. The crude product was crystallized in diethyl ether to give 2.5 g (yield 86 %) white powder of 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic amide.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.13 (t, 3H, J=6.8 Hz), 2.80-2.90 (m, 1H), 3.05-3.14 (m, 6H), 3.36-3.56 (m, 2H), 3.84-3.91 (m, 1H), 4.14 (t, 2H, J=6.5 Hz), 5.38 (s br, 1 NH), 6.42 (s br, 1 NH), 6.80 (dm, 2H, J=8.8 Hz, unresolved), 7.15 (dm, 2H, J=8.8 Hz, unresolved), 7.19-7.27 (m, 2H), 7.34 (dm, 2H, J=8.1 Hz, unresolved).

^{13}C-NMR (75 MHz; $CDCl_3$): δ 15.2, 35.2, 37.3, 38.0, 66.6, 68.1, 81.4, 114.2, 122.0, 129.7, 130.58, 130.64, 138.0, 147.8, 157.3, 175.2.

Example 6. 2-Cyano-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester

A mixture of 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate (2 g; 6.24 mmole), ethyl cyanoacetate (1.41 g; 12.48 mmole) and sodium acetate (1.34 g; 15.6 mmole) was heated to 120° C. The mixture that melted upon heating was then allowed to cool to 40° C. Dichloromethane was added and the solution was washed with water and brine, dried (sodium sulfate), filtered and the solvent was evaporated *in vacuo* to give a crude product which was purified by chromatography on silica gel using heptan:ethyl acetate (gradient 9:1 to 1:1) as eluent and then by crystallization to give 1.98 g (yield 77 %)of the title compound.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.37 (t, 3H, J=7.1 Hz), 3.13 (t, 2H, J=6.8 Hz), 3.13 (s, 3H),4.24 (t, 2H, J=6.8 Hz), 4.35 (q, 2H, J=7.1 Hz), 6.95 (dm, 2H, J=9 Hz, unresolved), 7.23 (dm, 2H, J=9 Hz, unresolved), 7.32 (dm, 2H, J=9 Hz, unresolved), 7.97 (dm, 2H, J=9 Hz, unresolved), 8.15 (s, 1H).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.2, 34.9, 37.4, 62.4, 68.6, 99.6, 115.2, 116.1, 122.1, 124.6, 130.5, 133.6, 137.3, 148.0, 154.3, 162.8, 163.1.

Example 7. 2 Cyano-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester

A mixture of 2-cyano-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester (1.69 g; 4.07 mmole) and diethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate (2.06 g; 8.14 mmole) was slowly heated to more than 190° C under vacuum and thereafter allowed to cool to room temperature. The crude product was purified by chromatography on silaca gel using heptan:ethyl acetate (gradient 2:1 to 1:1) as eluent to give 1.55 g (yield 91 %) of the desired product.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 2.96-3.16 (m, 6H), 3.66-3.72 (m, 1H), 4.05 (t, 2H, J=6.8 Hz), 4.13 (q, 2H, J=7 Hz), 6.73 (dm, 2H, J=8.5 Hz, unresolved), 7.09-7.19 (m, 4H), 7.25 (dm, 2H, J=8.5 Hz, unresolved).
^{13}C-NMR (100 MHz; $CDCl_3$): δ 13.4, 34.3, 34.5, 36.7, 39.3, 114.3, 116.0, 121.5, 127.2, 129.6, 130.1, 137.4, 147.5, 157.7, 165.2.

Example 8. 2-Cyano-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid

A mixture of 2-cyano-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester (0.9 g; 2.16 mmole), lithium hydroxide hydrate (0.12 g; 2.86 mmole), methanol (5 ml), water (5 ml) and tetrahydrofuran (10 ml) was stirred for 30 minutes at room temperature. Water was added and the mixture was washed with diethyl ether. The water phase was acidified with hydrochloric acid and extracted with ethyl acetate. The organic phase was dried (sodium sulfate), filtered and evaporated *in vacuo*. The crude product was purified by crystallization in diisopropyl ether to give 0.56 g (yield 67 %) of the desired product.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 3.02-3.3 (m, 7H), 3.7-3.8 (m, 1H), 4.15 (t, 2H, J=6.7), 6.8-6-9 (m, 2H), 7.15-7.27 (m, 4H), 7.27-7.4 (m, 2H), 8.67 (s, 1 OH).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 34.8, 35.0, 37.3, 39.9, 68.2, 114.9, 115.6, 122.0, 127.0, 130.2, 130.6, 137.8, 147.8, 158.3, 170.0.

Example 9. 2-Cyano-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid

2-Cyano-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester (0.201 g; 0.483 mmole), lithium hydroxide (0.04 g; 1.67 mmole), methanol (2.3 ml) and water (2.3 ml) was stirred at 40° C for 23 hours. More water was added, methanol was removed by evaporation *in vacuo* and the mixture was acidified using potassium hydrogen sulfate. The mixture was extracted with ethyl acetate and the organic phase was dried (sodium sulfate), filtered and evaporated *in vacuo*. The crude products were purified on preparative HPLC using acetonitrile (gradient 30-60 %):0,1 M ammonium acetate, the fractions were acidified with potassium hydrogen sulfate, extracted with ethyl acetate and the organic phases were evaporated *in vacuo* to give 7 mg of 2-cyano-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid and 21,8 mg of 2-cyano-3-{4-[2-(4-hydroxyphenyl)ethoxy]phenyl}acrylic acid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.11 (t, 2H, J=6.8 Hz), 3.12 (s, 3H), 4.23 (t, 2H, J=6.8 Hz), 6.94 (dm, 2H, J=9 Hz, unresolved), 7.22 (dm, 2H, J=8.5 Hz, unresolved), 7.31 (dm, 2H, J=8.5 Hz, unresolved), 7.95 (dm, 2H, J=9 Hz, unresolved), 8.13 (s, 1H).
^{13}C-NMR (100 MHz; $CDCl_3$): δ 34.9, 37.4, 68.6, 99.6, 115.2, 116.3, 122.1, 124.5, 130.5, 133.6, 137.3, 148.0, 154.7, 162.8, 164.9.

Example 10. 2-{4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]benzylidene}malonic acid dimethyl ester

A solution of titanium tetrachloride (4.82 g; 25.4 mmole) and carbon tetrachloride (6.35 ml) was added to dry tetrahydrofuran (50.8 ml) at 0° C under argon. To the mixture was added a solution of 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate (4.07 g; 12.7

mmole) in dry tetrahydrofuran (6.35 ml) and then dimethyl malonate (1.68 ml, 12.7 mmole). Finally pyridine (4.02 g; 50.8 mmole) in tetrahydrofuran (8.9 ml) was added during 3 hours. The reaction mixture was then stirred at room temperature for 15 hours. Water was added and the product was extracted with a mixture of diethyl ether and ethyl acetate, the organic phase was washed with water, the water phase was extracted with dichloromethane, the organic phases were combined, dried (sodium sulfate), filtered and the solvents were evapoated *in vacuo* to give 5.34 g (yield 97 %) of 2-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]benzylidene}malonic acid dimethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.12 (t, 2H, J=7), 3.14 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 4.2 (t, 2H, J=7 Hz), 6.9 (dm, 2H, J=9 Hz, unresolved), 7.24 (dm, 2H, J=9 Hz, unresolved), 7.31-7.41 (m, 4H), 7.7 (s, 1H).
^{13}C-NMR (100 MHz; $CDCl_3$): δ 34.9, 37.3, 52.5, 52,6, 68.3, 114.9, 122.0, 122.9, 125.4, 130.5, 131.5, 137.5, 142.4, 147.9, 160.7, 164.8, 167.5.

Example 11. 2-{4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]benzyl}malonic acid dimethyl ester

2-{4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]benzylidene}malonic acid dimethyl ester (2.31 g; 5.32 mmole) was hydrogenated for 2.5 hours at atmospheric pressure in ethyl acetate (140 ml) and acetic acid (5 ml) using Pd/C (0.8 g) as catalyst and then filtered on hyflo. The solvent was evaporated *in vacuo*, dichloromethane and diluted sodium bicarbonate solution were added, the phases were seperated. The organic phase was washed with brine, dried (sodium sulfate), filtered and evaporated *in vacuo* to give 2.35 g (yield 100 %) of 2-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]benzyl}malonic acid dimethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.10(t, 2H, J=6.6 Hz), 3.14 (s, 3H), 3.17 (d, 2H, J=7.6 Hz), 3.64 (t, 1H, J=7.6), 3.71 (s, 6H), 4.15 (t, 2H, J=6.6 Hz), 6.81 (dm, 2H, J=8.8 Hz,

unresolved), 7.11 (dm, 2H, J=8.8 Hz, unresolved), 7.24 (dm, 2H, J=8.8 Hz, unresolved), 7.34 (dm, 2H, J=8.8 Hz, unresolved).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 33.9, 35.1, 36.0, 37.3, 52.5, 53.8, 68.2, 114.6, 121.9, 129.8, 130.0, 130.5, 137.9, 147.9, 157.5, 169.2.

Example 12. 2-Benzenesulfonyl-3-{4-[2-(4-methanesulfonyloxy-phenyl)ethoxy]phenyl}propanoic acid methyl ester

(a) Methanesulfonic acid 4-[2-(4-hydroxymethylphenoxy)ethyl]phenyl ester

Sodium boronhydride (0.40 g; 10.43 mmole) was added to suspension of 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate (6.69 g; 20.09 mmole) in ethanol (150 ml). After stirring at room temperature for 1 hour solid material was filtered off and the filtrate was evaporated *in vacuo*. Water was added and the product was extracted with ethyl acetate, the organic phase was dried (sodium sulfate), filtered and evaporated *in vacuo* to give 5.8 g (yield 86 %) of methanesulfonic acid 4-[2-(4-hydroxymethylphenoxy)-ethyl]phenyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.08-3.15 (m, 5H), 4.18 (t, 2H, J=6.8 Hz), 4.61 (s, 2H), 6.88 (dm, 2H, J=8.4 Hz, unresolved), 7.24 (dm, 2H, J=8.8 Hz, unresolved), 7.28 (dm, 2H, J=8.4 Hz, unresolved), 7.34 (dm, 2H, J=8.8 Hz, unresolved).

(b) Methanesulfonic acid 4-[2-(4-bromomethylphenoxy)ethyl]phenyl ester

Phosphorus tribromide (1.75 g; 6.49 mmole) was added to a solution of methanesulfonic acid 4-[2-(4-hydroxymethylphenoxy)ethyl]phenyl ester (2.08 g; 6.49 mmole) in dichloromethane (29 ml) at 0° C under argon. After stirring at 0° C for 2 hours and then at room temperature for 1 hour, the reaction mixture was poored onto ice and the the product was extracted with diethyl ether, dried (sodium sulfate), filtered and evapoerated *in vacuo*. The product was dissolved in dichloromethane, filtered and evaporated *in vacuo* to give

2.18 g (yield 87 %) of methanesulfonic acid 4-[2-(4-bromomethylphenoxy)ethyl]phenyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.08-3.14 (m, 5H), 4.18 (t, 2H, J=6.8 Hz), 4.5 (s, 2H), 6.85 (dm, 2H, J=8.4 Hz, unresolved), 7.24 (dm, 2H, J=8.8 Hz, unresolved), 7.28-7.37 (m, 4H).

(c) 2-Benzenesulfonyl-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid methyl ester

Potassium carbonate (0.60 g; 4.38 mmole) and triethylbenzylammonium chloride (0.06 g; 0.26 mmole) were added to a solution of methylphenylsulphonyl acetate (0.63 g; 2.92 mmole) in acetonitrile (2 ml). After 20 minutes methanesulfonic acid 4-[2-(4-bromomethylphenoxy)ethyl]phenyl ester (1.05 g; 2.92 mmole) in acetonitrile (0.7 ml) was added. After stirring at room temperature over night water and hydrochloric acid were added. When pH=1, dichloromethane was added, the phases were seperated (by adding brine), the organic phase was twice washed with water and brine, dried (sodium sulfate), filtered and solvent was evaporated *in vacuo*. Purification by chromatography on silica gel using heptane:ethyl acetate (1:1) as eluent gave 1.18 g (yield 78 %) of the desired product.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 3.08 (t, 2H, J=6.5 Hz), 3.13 (s, 3H), 3.16-3.24 (m, 1H), 3.32-3.39 (m, 1H), 3.53 (s, 3H), 4.13 (t, 2H, J=6.8 Hz), 4.2-4.26 (m, 1H), 6.8 (apparent d, 2H, J=8.5 Hz) 7.05 (apparent d, 2H, J=8.5 Hz), 7.24 (apparent d, 2H, J=8.5 Hz), 7.35 (apparent d, 2H, J=8.5 Hz), 7.61 (apparent t, 2H, J=8 Hz), 7.72 (apparent t, 1H, J=8 Hz), 7.94 (apparent t, 2H, J=8 Hz).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 31.5, 34.7, 36.9, 52.6, 67.9, 72.0, 114.6, 121.7, 127.2, 128.9 (2 signals overlapping), 129.6, 130.3, 134.2, 136.7, 137.6, 147.6, 157.6, 165.5.

Example 13. 2-Ethoxy-3-{3-[3-(4-methanesulfonyloxyphenyl)propoxy]phenyl}propanoic acid ethyl ester

(a) 3-(3-Benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester

Tetramethylguanidine (6.5 g; 56.6 mmole) was slowly added to a solution of 3-benzyloxybenzaldehyde (11.7 g; 55 mmole) and ethoxy ethoxycarbonylmethyl-triphenylphosphonium chloride (20.1 g; 46.8 mmole) in dichloromethane (200 ml) at 0° C. After stirring at room temperature over night the solvent was evaporated *in vacuo*. Diethyl ether was added and material that did not go into solution was filtered off. The filtrate was washed with sodium bicarbonate solution, dried (magnesium sulfate), filtered and the solvent was evaporated *in vacuo*. The residue was purified by chromatography on silica gel using dichloromethane:tetrahydrofuran (0,5 %) as eluents. The remaining aldehyde was removed by stirring with sodium bisulfite in water and diethyl ether for 2 days. The phases were separated and the organic phase was evaporated *in vacuo* to give 10.5 g (yield 69 %) of 3-(3-benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1,4 (m, 6H), 4.02 (q, 2H), 4.32 (q, 2H), 5.12 (s, 2H), 6.97 (unresolved, 2H), 7.3-7.5 (m, 7H), 7.7 (unresolved, 1H).

^{13}C-NMR (75 MHz; $CDCl_3$): δ 14.3, 15.6, 61.2, 67.7, 69.9, 115.6, 116.1, 123.2, 123.7, 127.4, 128.0, 128.6, 129.4, 135.0, 137.0, 144.9, 158.8, 164.6.

(b) 2-Ethoxy-3-(3-hydroxyphenyl)propanoic acid ethyl ester

3-(3-Benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester (10.4 g; 31.8 mmole) was hydrogenated at atmospheric pressure in ethyl acetate using Pd/C (dry, 10 %) as catalyst. The reaction mixture was filtered through celite and the solvent was evaporated *in vacuo*. The starting material was not completely consumed, therefor the hydrogenation was repeated to give 7 g (yield 92 %) of 2-ethoxy-3-(3-hydroxyphenyl)propanoic acid ethyl ester.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.15 (t, 3H), 1.22 (t, 3H), 2.95 (m, 2H), 3.4 (m, 1H), 3,6 (m, 1H), 4.05 (m, 1H), 4.15 (q, 2H).
^{13}C-NMR (75 MHz; $CDCl_3$): δ 14.1, 15.0, 39.2, 61.2, 66.4, 80.2, 113.9, 116.5, 121.2, 129.4, 137.2, 138.5, 156.0.

(c) 3-(4-Methanesulfonyloxyphenyl)propylmethanesulfonate

Methanesulfonyl chloride (25 g; 220 mmole) dissolved in dichloromethane was slowly added to a solution of 3-(4-hydroxyphenyl)-1-propanol (15 g; 100 mmole) and triethyl amine (25 g; 250 mmole) in dichloromethane (150 ml). Stirring over night and evaporation of the solvent *in vacuo* gave 28.5 g (yield 92.4 %) of 3-(4-methanesulfonyloxyphenyl)-propylmethanesulfonate.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.1 (q, 2H), 2.8 (t, 2H), 3.0 (s, 3H), 3.15 (s, 3H), 4.25 (t, 2H), 7.23-7.27 (m, 4H).
^{13}C-NMR (100 MHz; $CDCl_3$): δ 31.7, 32.1, 38.4, 38.5, 69.8, 123.2, 131.1, 140.9, 148.7.

(d) 2-Ethoxy-3-{3-[3-(4-methanesulfonyloxyphenyl)propoxy]phenyl}propanoic acid ethyl ester

3-(4-Methanesulfonyloxyphenyl)propylmethanesulfonate (1.905 g; 6.18 mmole) dissolved in actonitrile (13 ml) was dropped into a mixture of 2-ethoxy-3-(3-hydroxyphenyl)-propanoic acid ethyl ester (1.47 g; 6.18 mmole) and potassium carbonate (2.56 g; 18.54 mmole) in acetonitrile (15 ml). The mixture was refluxed for 5 hours, then the solvent was evaporated *in vacuo* and water was added. The product was extracted twice with dichloromethane, dried (sodium sulfate), filtered and the solvent was evaporated *in vacuo*. Purification by chromatography on silica gel using petroleum ether:diethyl ether (gradient 33 % to 100 % diethyl ether) gave 1.80 g (yield 65 %) of 2-ethoxy-3-{3-[3-(4-methanesulfonyloxyphenyl)propoxy]phenyl}propanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 1.24 (t, 3H, J=7.3 Hz), 2.05-2.14 (m, 2H), 2.84 (t, 2H, J=7.5 Hz), 2.97-3.01, (m, 2H), 3.14 (s, 3H), 3.33-3.42 (m, 1H), 3.58-3.66 (m, 1H), 3.96 (t, 2H, J=6 Hz), 4.0-4.05 (m, 1H), 4.15-4.23 (m, 2H), 6.74-6.87 (m, 3H), 7.17-7.24 (m, 3H), 7.25-7.30 (m, 2H).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.2, 15.0, 30.7, 31.6, 37.2, 39.4, 60.8, 66.2, 66.5, 80.1, 112.8, 115.6, 121.8, 121.9, 129.2, 130.0, 138.8, 141.0, 147.4, 158.8, 172.4.

Example 14. 2-Ethoxy-3-[3-(3-{4-methanesulfonyloxyphenyl}propoxy)phenyl]propanoic acid

Lithium hydroxide hydrate (91.1 mg; 2.7 mmole) in water (6.6 ml) was slowly added to a solution of 2-ethoxy-3-{3-[3-(4-methanesulfonyloxyphenyl)propoxy]phenyl}propanoic acid ethyl ester (0.889 g; 1.97 mmole) in tetrahydrofuran (9 ml). After stirring at room temperature for 5 hours tetrahydrofuran was removed by evaporation *in vacuo*. The water residue was washed with diethyl ether and ethyl acetate, the water phase was acidified with potassium hydrogen sulfate (1M), and the product was extracted with ethyl acetate and dichloromethane, dried (sodium sulfate), filtered and the solvent was evaporated *in vacuo* to give 0.91 g of 2-ethoxy-3-[3-(3-{4-methanesulfonyloxyphenyl}propoxy)-phenyl]propanoic acid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.20 (t, 3H, J=7.1 Hz), 2.05-2.15 (m, 2H), 2.84 (t, 2H, J=7.6 Hz), 2.95-3.03, (m, 1H), 3.11-3-17 (m, 4H), 3.46-3.65 (m, 2H), 3.95 (t, 2H, J=6.1 Hz), 4.09-4.14 (m, 1H), 6.77-6.81 (m, 2H), 6.82 (dm, 1H, J=7.81 Hz, unresolved), 7.19-7.29 (m, 5H).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 15.0, 30.7, 31.6, 37.3, 38.6, 66.5, 67.0, 79.5, 113.0, 115.6, 121.88, 121.90, 129.4, 130.0, 138.0, 141.0, 147.4, 158.9, 173.9.

Example 15. 3-{4-[2-(4-*Tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester

(a) 3-(4-Benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester

Tetramethylguanidine (42.3 g; 0.37 mmole) was slowly added to a solution of 4-benzyloxybensaldehyde (75.6 g; 0.36 mmole) and ethoxy ethoxycarbonylmethyl-triphenylphosphonium chloride (130.7 g; 0.304 mmole) dissolved in chloroform (800 ml) at 0° C. After stirring at room temperature over night, the solvent was evaporated *in vacuo*. The residue was dissolved in diethyl ether, insoluble material was filtered off and the filtrate was washed with sodium bicarbonate and dried (magnesium sulfate). The procedure was repeated once and therafter the crude product was stirred over night with a sodium bisulfite saturated water solution. The solid material was filtered off, the product was extracted with diethyl ether, dried (magnesium sulfate) and the solvent was evaporated *in vacuo* to give 85 g (yield 73 %) of 3-(4-benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.35 (m, 6H), 4.0 (q, 2H), 4.3 (q, 2H), 5.05 (s, 2H), 6.95 (s+m unresolved, 1+3H), 7.3-7.45 (m, 5H), 7.75 (d, 2H).
^{13}C-NMR (125 MHz; $CDCl_3$): δ 14.4, 15.6, 61.0, 67.5, 70.0, 114.8, 124.0, 126.7, 127.5, 128.1, 128.6, 131.7, 136.7, 143.1, 159.2, 165.0.

(b) 2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester

3-(4-Benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester (62 g; 0.19 mmole) was hydrogenated in ethyl acetate (400 ml) at atmospheric pressure using Pd/C (10 %) as catalyst. The mixture was filtered through celite and evaporated *in vacuo* to give 45.6 g (yield 100 %) of 2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 1.23 (t, 3H, J=7 Hz), 2.95 (d, 2H, J=6.6 Hz), 3.35-3.42 (m, 1H), 3.58-3.64 (m, 1H), 4.0 (t, 1H, J=6.6 Hz), 4.17 (q, 2H, J=7

Hz), 5.97 (s, 1 OH), 6.74 (dm, 2H, J=8.5 Hz, unresolved), 7.08 (dm, 2H, J=8.5 Hz, unresolved).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 14.0, 14.8, 38.3, 61.0, 66.1, 80.3, 115.1, 128.2, 130.3, 154.8, 173.0.

(c) 4-(2-Hydroxyethyl)phenylcarbamic acid tert-butyl ester

Di-tert-butyl dicarbonate (7.95 g; 36 mmole) was added to a mixture of p-aminophenethyl alcohol (5 g; 36 mmole) in tetrahydrofuran at 0° C. After stirring at room temperature over night, the solvent was evaporated *in vacuo* to give 8 g (yield 94 %) of 4-(2-hydroxyethyl)phenylcarbamic acid tert-butyl ester.

^{1}H-NMR (400 MHz; DMSO-d_6): δ 1,5 (s, 9H), 2,65 (dd, 2H), 3,55 (dd, 2H), 4,6 (s, br, 1 OH), 7,1 (unresolved, 2H), 7,35 (unresolved, 2H), 9,1 (s, 1 NH).

^{13}C-NMR (100 MHz; DMSO-d_6): δ 28.3, 38.6, 62.5, 78.9, 118.3, 129.1, 133.2, 136.6, 153.0.

(d) 3-{4-[2-(4-*T*ert-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester

4-(2-Hydroxyethyl)phenylcarbamic acid tert-butyl ester (1.03 g; 4.34 mmole) and 2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester (1.03 g; 4.34 mmole) were dissolved in dichloromethane under argon at room temperature. Azodicarbonyl dipiperidine (1.65 g; 6.5 mmole) and thereafter triphenylphosphine (1.37 g; 5.2 mmole) were added. After stirring at room temperature for 6 hours the solvent was evaporated *in vacuo*. Purification by chromatography on silica gel using heptan:ethyl acetate (2:1) as eluent gave 1.78 g (yield 89%) of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]-phenyl}-2-ethoxypropanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 1.23 (t, 3H, J=7 Hz), 1.53 (s, 9H), 2.94-2.97 (m, 2H), 3.03 (t, 2H, J=7.1 Hz), 3.31-3.40 (m, 1H), 3.56-3.65 (m, 1H), 3.95-4.0 (m, 1 H), 4.11 (t, 2H, J=7.1 Hz), 4.17 (q, 2H, J=7 Hz), 6.60 (s, 1NH), 6.81 (dm, 2H, J=8.3 Hz, unresolved), 7.15 (dm, 2H, J=8.3 Hz, unresolved), 7.20 (dm, 2H, J=8.3 Hz, unresolved), 7.31 (dm, 2H, J=8.3 Hz, unresolved).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.1, 15.0, 28.3, 35.0, 38.4, 60.7, 66.1, 68.6, 80.26, 80.32, 114.3, 118.7, 128.2, 129.4, 130.3, 132.8, 136.7, 152.8, 157.5, 172.4.

Example 16. 3-{4-[2-(4-*Tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid

Lithium hydroxide hydrate (77 mg; 1.85 mmole) in water (5.5 ml) was slowly added to a solution of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester (0.77 g; 1.68 mmole) in tetrahydrofuran (7.6 ml). After stirring at room temperature for 4 hours the reaction mixture was kept in a freezer for 4 days. Tetrahydrofuran was removed by evaporation *in vacuo*. More water was added and the mixture was acidified with hydrochloric acid to pH1. The product was extracted with ethyl acetate, washed twice with water, dried (sodium sulfate), filtered and the solvent was evaporated *in vacuo* to give 0.712 g of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-2-ethoxypropanoic acid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.18 (t, 3H, J=7 Hz), 1.54 (s, 9H), 2.93-3.10 (m, 4H), 3.36-3.45 (m, 1H), 3.60-3.69 (m, 1H), 4.02-4.07 (m, 1 H), 4.12 (t, 2H, J=7 Hz), 6.83 (dm, 2H, J=8.8 Hz, unresolved), 7.15-7.23 (m, 4H), 7.27-7.34 (m, 2H), 10.28 (bs, 1NH).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 15.0, 28.3, 35.2, 38.0, 66.7, 68.8, 79.9, 80.7, 114.6, 119.1, 129.0, 129.4, 130.4, 133.1, 136.8, 153.2, 157.8, 175.3.

Example 17. 2-Ethoxy-3-{4-[2-(4-methanesulfonylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester

(a) 3-{4-[2-(4-Aminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester

4-Aminophenethyl alcohol (1.39 g; 10.2 mmole) and 2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester (2.42 g; 10.2 mmole) were dissolved in dichloromethane (35 ml) under argon at room temperature. Azodicarbonyl dipiperidine (3.85 g; 15.2 mmole) and thereafter triphenylphosphine (3.20 g; 12.2 mmole) were added. After stirring at room temperature for 1 minute dichloromethane (30 ml) was added and after 21 hours the solvent was evaporated *in vacuo*. Purification by chromatography on silica gel using heptan:ethyl acetate (3:2) as eluent gave 3.12 g (yield 86%) of 3-{4-[2-(4-aminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.18 (t, 3H, J=7 Hz), 1.24 (t, 3H, J=7 Hz), 2.95-3.02 (m, 4H), 3.31-3.42 (m, 1H), 3.58-3.67 (m, 3H), 3.96-4-02 (m, 1H), 4.10 (t, 2H, J=7 Hz), 4.13 (q, 2H, J=7 Hz), 6.66 (dm, 2H, J=8.3 Hz, unresolved), 6.83 (dm, 2H, J=8.3 Hz, unresolved), 7.08 (dm, 2H, J=8.3 Hz, unresolved), 7.16 (dm, 2H, J=8.3 Hz, unresolved). ^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.1, 15.0, 34.9, 38.4, 60.7, 66.1, 69.0, 80.3, 114.3, 115.2, 127.9, 129.1, 129.7, 130.3, 144.8, 157.6, 172.5.

(b) 2-Ethoxy-3-{4-[2-(4-methanesulfonylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester

Triethylamine (0.544 g; 2.99 mmole) and thereafter methanesulfonyl chloride (0.392 g; 2.99 mmole) were added to a solution of 3-{4-[2-(4-aminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester (0.89 g; 2.49 mmole) in dichloromethane (8,9 ml) at 0° C. After stirring at room temperature for 20 hours the reaction mixture was poured onto hydrochloric acid in ice. Dichloromethane was added, the phases were seperated and the organic phase was washed with water, dried (sodium sulfate), filtered and the solvent was

evaporated *in vacuo*. Purification by chromatography on silica gel using heptan:ethyl acetate (3:2) as eluent gave 0.78 g (yield 72 %) of 2-ethoxy-3-{4-[2-(4-methanesulfonyl-aminophenyl)ethoxy]phenyl}propanoic acid ethyl ester.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.18 (t, 3H, J=7 Hz), 1.25 (t, 3H, J=7 Hz), 2.96-2.99 (m, 2H), 3.01 (s, 3H), 3.07 (t, 2H, J=7 Hz), 3.34-3.43 (m, 1H), 3.59-3.66 (m, 1H), 3.98-4-03 (m, 1H), 4.13-4.22 (m, 4H), 6.83 (dm, 2H, J=8.8 Hz, unresolved), 7.16 (dm, 2H, J=8.8 Hz, unresolved), 7.22 (dm, 2H, J=8.5 Hz, unresolved), 7.28 (dm, 2H, J=8.5 Hz, unresolved).
^{13}C-NMR (125 MHz; $CDCl_3$): δ 14.1, 15.0, 35.0, 38.3, 39.0, 60.7, 66.1, 68.3, 80.2, 114.2, 121.2, 129.3, 130.1, 130.3, 135.1, 135.7, 157.4, 172.5.

Example 18. 2-Ethoxy-3-{4-[2-(4-methanesulfonylaminophenyl)ethoxy]phenyl}propanoic acid

2-Ethoxy-3-{4-[2-(4-methanesulfonylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester (0.554 g; 1.27 mmole) was dissolved in tetrahydrofuran (5.7 ml). Lithium hydroxide hydrate (0.137 g; 3,26 mmole) was dissolved in water and added in portions during 30 hours at room temperature (the reaction mixture was kept at 4° C for 14/30 hours). Tetrahydrofuran was evaporated *in vacuo*. The water residue was washed with ethyl acetate, acidified with hydrochloric acid (1N) to pH1-2 and the product was extracted with ehtyl acetate. The organic phase was washed with brine, dried (sodium sulfate), filtered and the solvent was evaporated *in vacuo* to give 0.54 g (yield 100 %) of 2-ethoxy-3-{4-[2-(4-methanesulfonylaminophenyl)ethoxy]phenyl}propanoic acid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 2.93-3.0 (m, 4H), 3.0-3.09 (m, 3H), 3.37-3.47 (m, 1H), 3.59-3.68 (m, 1H), 4.03-4-08 (m, 1H), 4.12 (t, 2H, J=7 Hz), 6.82 (dm, 2H, J=8.8 Hz, unresolved), 7.14-7.29 (m, 6H), 7.40 (s, 1NH), 9.02 (bs, 1H).
^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.9, 35.0, 37.8, 39.0, 66.5, 68.3, 79.6, 114.3, 121.2, 128.8, 130.0, 130.3, 135.1, 135.6, 157.4, 176.3.

Examples 19 and 20. 2-Ethoxy-3-{4-[2-(4-methylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester and 3-{4-[2-(4-dimethylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester

Formaldehyde (0,273 ml, 3,36 mmole, 37 wt. % solution in water) and Pd/C (100 mg, 10 %) were added to a solution of 3-{4-[2-(4-aminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester (0,96 g, 2,69 mmole) in ethyl acetate (15 ml) and then hydrogenated at atmospheric pressure and room temperature for 4 hours. Filtration on celite and purification by chromatography on silica gel using heptan:ethyl acetate (gradient 4:1 to 1:1) as eluent gave 0,49 g (yield 49 %) of 2-ethoxy-3-{4-[2-(4-methylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester and 0,24 g (yield 23 %) of 3-{4-[2-(4-dimethylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester

2-Ethoxy-3-{4-[2-(4-methylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester
^{1}H NMR (400 MHz; $CDCl_3$): δ/ppm 7.13 (d, J=8.5 Hz, 2H), 7.10 (d, J=8.5 Hz, 2H), 6.81 (d, J=8.5 Hz, 2H), 6.58 (d, J=8.5 Hz, 2H), 4.16 (q, J=7.1 Hz, 2H), 4.08 (t, J=7.4 Hz, 2H), 3.96 (dd, J=7.3 and 5.9 Hz, 1H), 3.59 (dq, J=9.2 and 7.0, 1H), 3.34 (dq, J=9.2 and 7.0 Hz, 1H), 2.98 (t, J=7.4 Hz, 2H), 2.94 (m, 2H),
^{13}C NMR (100 MHz; $CDCl_3$): δ/ppm 172.6, 157.7, 147.9, 130.3, 129.7, 129.1, 126.8, 114.3, 112.6, 80.5, 69.2, 66.2, 60.7, 38.5, 34.9, 30.9, 15.1, 14.2.

3-{4-[2-(4-Dimethylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester
^{1}H NMR (500 MHz; CD_3OD): δ 7.12 (d,J=8.6 Hz, 2H), 7.10 (d, J=8,6 Hz, 2H), 6.80 (d, J=8.6 Hz, 2H), 6.75 (d, J=8.6 Hz, 2H), 4.11 (q, J=7.1 Hz, 2H), 4.07 (t, J=7.0 Hz, 2H), 4.01 (dd, J=7.5 and 5.7 Hz, 1H), 3.55 (m, 1H), 3.36 (m, 1H), 2.93 (t, J=7.0 Hz, 2H), 2.91 (m, 2H), 2.87 (s, 6H), 1.17 (t, J=7.1 Hz, 3H), 1.12 (t, J=7.0 Hz, 3H).

Example 21. 3-{4-[2-(4-Dimethylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid

Lithium hydroxide hydrate (38 mg; 0.90 mmole) dissolved in water (2 ml) was added to a solution of 3-{4-[2-(4-dimethylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester (232 mg; 0.60 mmole) in tetrahydrofuran (6 ml). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was acidified with 2 M hydrochloric acid to pH 5. Tetrahydrofuran was evaporated *in vacuo*, water (5 ml) was added and the product was extracted with ethyl acetate (10 + 5 ml), dried (sodium sulfate) and the solvent was evaporated *in vacuo*. Purification by filtration on silica gel gave 180 mg (yield 84 %) of 3-{4-[2-(4-dimethylamino-phenyl)ethoxy]phenyl}-2-ethoxypropanoic acid .

^{1}H NMR(600 MHz; $CDCl_3$): δ 7.15 (d, J=8.3 Hz, 2H), 7.13 (d, J=8.3 Hz, 2H), 6.81 (d, J=8.3 Hz, 2H), 6.74 (d, J=8.3 Hz, 2H), 4.12 (t, J=7.3 Hz, 2H), 4.03 (m, 1H), 3.59 (m, 1H), 3.42 (m,1H), 3.06 (dd, J=14.1 and 3.8, 1H), 2.99 (t, J=7.3 Hz, 2H), 2.93 (m, 1H), 2.92 (s, 6H), 1.16 (t, J=7.0 Hz, 3H).
^{13}C NMR(150 MHz; $CDCl_3$): δ 174.9, 157.8, 149.4, 130.4, 129.6, 128.6, 126.6, 114.4, 113.3, 79.9, 69.1, 66.8, 41.0, 37.8, 34.8, 15.0.

Example 22. 2-{4-[2-(4-Phenylsulfanylphenyl)ethoxy]benzyl}butanoic acid

(a) 2-(4-Hydroxybenzyl)butanoic acid methyl ester

2-[(4-Hydroxyphenyl)methylene]-butanoic acid (10.48 g, 54.5 mmol) was refluxed 24 hours in a solution of 1% sulphuric acid in methanol (150 ml). The solvent was evaporated and water (100 ml) was added. The water phase was extracted with ethyl acetate twice, the organic phases were combined and was dried (magnesiumsulfate) and solvent were evaporated *in vacuo*. The crude product (9 g, 43.6 mmole of it) was used directly in the next step without further purification and identification.

It was hydrogenated in methanol using palladium on charcoal (5 %, 3 g) as catalyst. The mixture was filtered through celite and solvent was evaporated. Purification by chromatography on silica gel using dichloromethane:metanol (gradient 0,5-100 % methanol) as eluent gave 6,8 g (yield 60 % over two steps) of 2-(4-hydroxybenzyl)-butanoic acid methyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 0.91(t, 3H, J=7.7 Hz), 1.55-1.84 (m, 2H), 2.57 (m, 1H), 2.68 (dd, 1H, J=6.2 Hz and 6.6 Hz), 2.82 (dd, 1H, J=6.2 Hz and 6.6 Hz), 3.61 (s, 3H), 5.58 (s, 1 OH), 6.71 (d, 2H, J=8.4 Hz), 6.99 (d, 2H, J=8.4 Hz).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 11.73, 25.09, 37.31, 49.57, 51.47, 115.22, 115.22, 129.87, 129.87, 131.26, 154.21, 176.55.

(b) 2-{4-[2-(4-Phenylsulfanylphenyl)ethoxy]benzyl}butanoic acid

2-(4-Phenylsulfanylphenyl)ethanol (0.5 g, 2.17 mmole), azodicarbonyl dipiperidine (0.66 g, 2.6 mmole) and triphenylphosphine (0.68 g, 2.6 mmole) were dissolved in dichloromethane (20 ml) at room temperature. After stirring for 10 minutes 2-(4-hydroxybenzyl)butanoic acid methyl ester (0.54 g, 2.6 mmole) dissolved in dichloromethane (5 ml) was added. After stirring at room temperature over night more of azodicarbonyl dipiperidine (0.33 g) and more of triphenylphosphine (0.34 g) were added. Solid material was filtered off after 2 hours and the filtrate was evaporated *in vacuo*. Purification by chromatography on silica gel using heptan:ethyl acetate (5:1) as eluent gave 0.638 g (yield 70%) of 2-{4-[2-(4-phenylsulfanylphenyl)ethoxy]benzyl}butanoic acid.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.33-7.20 (m, 9H), 7.05 (d, J=8.3 Hz, 2H), 6.79 (d, J=8.3 Hz, 2H), 4.13 (t, J=7.0 Hz, 2H), 3.60 (s, 3H), 3.05 (t, J=7.0, 2H) 2.86, (dd, J=13.7 and 8.4 Hz, 1H), 2.68 (dd, J=13.7 and 6.5 Hz, 1H), 2.54 (m,1H), 1.59 (m, 2H), 0.90 (t, J=7.3 Hz, 3H).

Example 23. 2-{4-[2-(4-Phenylsulfanylphenyl)ethoxy]benzyl}butanoic acid

Sodium hydroxide (3 ml, 1M) was slowly added to a solution of 2-{4-[2-(4-phenylsulfanylphenyl)ethoxy]benzyl}butanoic acid (0.59 g, 1.4 mmole) in dioxan (12 ml). The reaction mixture was stirred at room temperature for 12 hours, then at 50° C for 4 hours. Then lithium hydroxide (50 mg) was added and the mixture was stirred at 70° C for 24 hours. The reaction mixture was acified with hydrochloric acid (6 M), water (20 ml) was added and the product was extracted with ethyl acetate (2 x 25 ml), washed with water (25 ml), dried (sodium sulfate) and the solvent was evaporated *in vacuo* to give 0.53 g (yield 93 %) of the desired product.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.34-7.28 (m, 7H), 7.24 (d, J=8.3 Hz, 2H), 7.10 (d, J=8.7 Hz, 2H), 6.82 (d, J=8.7 Hz, 2H), 4.15 (t, J=7.0 Hz, 2H), 3.08 (t, J=7.0 Hz, 2H), 2.93 (dd, J=13.9 and 7.7 Hz, 1H), 2.72 (dd, J=13.9 and 7.0 Hz, 1H), 2.58 (m, 1H), 1.63 (m, 2H), 0.97 (t, J=7.3 Hz, 3H).
^{13}C NMR (100 MHz): δ 181.3, 157.3, 137.7, 136.3, 133.2, 131.6, 131.3, 130.5, 129.9, 129.8, 129.1, 126.8, 114.5, 68.3, 49.0, 36.9, 35.4, 24.7, 11.6.

Example 24. 2-Acetyl-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester

2-Acetyl-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester was synthesised in the same way as 2-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]-benzylidene}malonic acid dimethyl ester in example 10 using 4-[2-(4-formyl-phenoxy)ethyl]phenylmethanesulfonate (2.19 g; 6,82 mmole) and ethylaceto acetate (0.93 g; 7.16 mmole). The reaction was complete after 3 hours. The crude product was purified by chromatography on silica gel using heptane:ethyl acetate (gradient 2:1 to 3:2) as eluents to give (1.83 g; yield 62 %) of a mixture of cis and trans of 2-acetyl-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester, slightly polluted by starting material.

(Cis or trans) 2-acetyl-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.33 (t, 3H, J=7 Hz), 2.4 (s, 3H), 3.12 (t, 2H, J=6.7 Hz), 3.14 (s, 3H), 4.22 (t, 2H, J=6.7 Hz), 4.37 (q, 2H, J=7.2 Hz), 6.9 (dm, 2H, J=8.5 Hz, unresolved), 7.25 (dm, 2H, J=8.5 Hz, unresolved), 7.35 (dm, 2H, J=8.5 Hz, unresolved), 7.43 (dm, 2H, J=8.5 Hz, unresolved), 7.51 (s, 1H).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 13.8, 26.2, 34.7, 37.1, 61.5, 68.2, 114.7, 121.9, 125.3, 130.4, 131.6, 132.2, 137.4, 140.8, 147.8, 160.7, 168.1, 194.6.

(Trans or cis) 2-acetyl-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.36 (t, 3H, J=7 Hz), 2.41 (s, 3H), 3.14 (t, 2H, J=6.5 Hz), 3.17 (s, 3H), 4.22 (t, 2H, J=6.5 Hz), 4.32 (q, 2H, J=7 Hz), 6.89 (dm, 2H, J=9 Hz, unresolved), 7.27 (dm, 2H, J=8.5 Hz, unresolved), 7.34-7.40 (m, 4H), 7.63 (s, 1H).

Example 25. 2-{4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]benzyl}-3-oxo-butanoic acid ethyl ester

2-Acetyl-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester (1.5 g; 3.47 mmole) was hydrogenated at atmospheric pressure in ethyl acetate (150 ml) using Pd/C as catalyst for 1.7 hours and then filtered on hyflo. The solvent was evaporated *in vacuo*, and the crude product was purified by chromatography on silica gel using heptan:ethyl acetate (gradient 3:1 to 1:1) as eluent to give (1.13 g; yield 75 %) of the desired product.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.15 (t, 3H, J=7.3 Hz), 2.13 (s, 3H), 2.98-3.08 (m, 7H), 3.75 (t, 1H, J=7.7 Hz), 4.04-4.14 (m, 4H), 6.76 (dm, 2H, J=8.5 Hz, unresolved), 7.06 (dm, 2H, J=8.5 Hz, unresolved), 7.18 (dm, 2H, J=8.5 Hz, unresolved), 7.25 (dm, 2H, J=8.5 Hz, unresolved).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 13.5, 29.0, 32.6, 34.5, 36.6, 60.8, 60.9, 67.6, 114.1, 121.5, 129.3, 129.9, 130.1, 137.5, 147.4, 156.9, 168.6, 202.1.

Example 26. 2-Ethoxy-3-{4-[2-(3-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester

(a) 2-(3-Methanesulfonyloxyphenyl)ethylmethanesulfonate

Methansulfonyl chloride (9.09g; 79.6 mmole) was slowly added to a solution of 3-hydroxyphenethyl alcohol (5 g; 36.2 mmole) and triethylamine (12.5 ml; 90.5 mmole) in dichloromethane at -10° C. The reaction mixture was stirred over night at room temperature and solid material was filtered off. The filtrate was washed with sodium bicarbonate solution and brine, dried (magnesium sulfate) and the solvent was evaporated *in vacuo* to give (9.3 g; yield 87 %) of 2-(3-methanesulfonyloxyphenyl)ethylmethanesulfonate.

(b) 2-Ethoxy-3-{4-[2-(3-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester

2-Ethoxy-3-{4-[2-(3-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester was synthesised in the same way as 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate in example 1 (b) using 2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester and 2-(3-methanesulfonyloxyphenyl)ethylmethanesulfonate.

Example 27. 2-Ethoxy-3-{4-[2-(3-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid

2-Ethoxy-3-{4-[2-(3-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid was synthesised in the same way as 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)-

phenyl]propanoic acid in example 2 using 2-ethoxy-3-{4-[2-(3-methanesulfonyloxy-phenyl)ethoxy]phenyl}propanoic acid ethyl ester.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.34 (m, 1H), 7.24 (m, 2H), 7.15 (m, 3H), 6.81 (d, J=8.6 Hz, 2H), 4.16 (t, J=6.7 Hz, 2H), 4.03 (dd, J= 7.7 and 4.3 Hz, 1H), 3.61 (m,1H), 3.42 (m,1H), 3.12 (s, 3H), 3.10 (t, J=6.7 Hz, 2H), 3.05 (dd, J=14.2 and 4.3 Hz, 1H), 2.94 (dd, J=14.2 and 7.7 Hz, 1H), 1.16 (t, J=7.0 Hz, 3H).
^{13}C NMR (100 MHz; $CDCl_3$): δ 174.7, 157.5, 149.3, 141.1, 130.5, 129.9, 128.8, 128.0, 122.6, 119.9, 114.4, 79.7,68.0, 66.8, 37.7, 37.3, 35.4, 15.0.

Example 28. 2-Ethoxy-3-{4-[2-(2-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester

(a) 2-(2-Methanesulfonyloxyphenyl)ethylmethanesulfonate

Methansulfonyl chloride (9 g; 79 mmole) was slowly added to a solution of 2-(2-hydroxyphenyl) ethanol (5 g; 36 mmole) and triethylamine (7.99 g; 79 mmole) in dichloromethane at 10° C. The reaction mixture was allowed to reach room temperature and poured onto hydrochloric acid and ice, The phases were seperated and the organic phase was washed with brine, dried and the solvent was evaporated. The residue crystallized on standing to give 9.4 g (yield 89 %) of 2-(2-methanesulfonyloxy-phenyl)ethylmethanesulfonate.

^{1}H NMR (300 MHz; $CDCl_3$): δ 2.85 (s, 3H), 3.15 (t, 2H), 3.25 (s, 3H), 4.4 (t, 2H), 7.2-7.35 (m, 4H).
^{13}C NMR (100 MHz; $CDCl_3$): δ 30.3, 37.2, 38.5, 69.0, 122.4, 127.6, 128.8, 129.6, 131.8, 147.5.

(b) 2-Ethoxy-3-{4-[2-(2-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester

2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester was alkylated with 2-(2-methanesulfonyloxyphenyl)ethylmethanesulfonate in an alkylating reaction in the same way as 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate in example 1 (b) to give 2-ethoxy-3-{4-[2-(2-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester.

Example 29. 2-Ethoxy-3-{4-[2-(2-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid

2-Ethoxy-3-{4-[2-(2-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester was hydrolyzed in the same way as 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl]propanoic acid in example 2 to give 2-ethoxy-3-{4-[2-(2-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (m, 1H), 7.35 (m, 1H), 7.27 (m, 2H), 7.15 (d, J=8.4 Hz, 2H), 6.82 (d, J=8.4 Hz, 2H), 4.19 (t, J=6.8 Hz, 2H), 4.03 (dd, J=7.7 and 4.3 Hz, 1H), 3.60 (m,1H), 3.42 (m,1H), 3.19 (s,3H), 3.18 (t, J=6.8 Hz, 2H), 3.06 (dd, J=14.2 and 4.3 Hz, 1H), 2.94 (dd, J=14.2 and 7.7 Hz, 1H), 1.6 (t, J=7.0 Hz, 3H).
^{13}C NMR (100 MHz; $CDCl_3$): δ 175.7, 157.5, 147.6, 131.5, 131.4, 130.5, 128.9, 128.1, 127.3, 122.1, 114.4, 79.7, 67.1, 66.8, 38.2, 37.8, 30.0, 15.0.

Example 30. 2-Ethoxy-3-{3-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester

(a) 4-[2-(3-Formylphenoxy)ethyl]phenylmethanesulfonate

3-Hydroxy-benzaldehyde was alkylated with 2-(4-methanesulfonyloxyphenyl)-ethylmethanesulfonate in an alkylation reaction in the same way as 4-[2-(4-

formylphenoxy)ethyl]phenylmethanesulfonate in example 1 (b) to give 4-[2-(3-formylphenoxy)ethyl]phenylmethanesulfonate.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.12 (t, 2H, J=6.7 Hz), 3.13 (s, 3H), 4.23 (t, 2H, J=6.7 Hz), 7.13-7.18 (m, 1H), 7.22-7.26 (m, 2H), 7.32-7.38 (m, 3H), 7.40-7.47 (m, 2H), 9.95 (s, 1H).
^{13}C-NMR (100 MHz; $CDCl_3$): δ 34.9, 37.2, 68.3, 112.7, 121.7, 121.9, 123.5, 128.6, 130.4, 137.5, 147.8, 159.1, 191.9.

(b) 2-Ethoxy-3-{3-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester

2-Ethoxy-3-{3-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester was made from 4-[2-(3-formylphenoxy)ethyl]phenylmethanesulfonate and ethoxy ethoxycarbonylmethyl-triphenylphosphonium chloride in a Wittig reaction in the same way as 2-ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester in example 1 (c).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.34 (2x t, 6H, J=7 Hz), 3.04-3.09 (m, 5H), 3.99 (q, 2H, J=7 Hz), 4.15 (t, 2H, J=7 Hz), 4.27 (apparently q, 2H, J=7 Hz), 6.8-6.85 (m, 1H), 6.92 (s, 1H), 7.1-7.25 (m, 3H), 7.28-7.33 (m, 3H), 7.39-7.42 (m, 1H).
^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.0, 15.3, 34.7, 36.8, 60.8, 67.4, 67.9, 115.2, 121.7, 122.7, 123.2, 129.1, 130.2, 134.7, 137.6, 144.7, 147.7, 158.3, 164.1.

(c) 2-Ethoxy-3-{3-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester

2-Ethoxy-3-{3-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}acrylic acid ethyl ester (3.69 g; 8.50 mmole) was hydrogenated for 3.5 hours at atmospheric pressure in ethyl acetate (70 ml) and acetic acid (0.5 ml) using Pd/C as catalyst and then filtered on hyflo. The solvent was evaporated *in vacuo*, dichloromethane and water were added, the phases were seperated. The organic phase was dried (sodium sulfate), filtered and evaporated *in*

vacuo to give 3.45 g (yield 93 %) of 2-ethoxy-3-{3-[2-(4-methanesulfonyloxyphenyl)-ethoxy]phenyl}propanoic acid ethyl ester.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.16 (t, 3H, J=7 Hz), 1.22 (t, 3H, J=7.1 Hz), 2.95-2.99 (m, 2H), 3.09 (t, 2H, J=6.7 Hz), 3.13 (s, 3H), 3.31-3.39 (m, 1H), 3.56-3.64 (m, 1H), 3.98-4.02 (m, 1H), 4.13-4.20 (m, 4H), 6.73-6.85 (m, 3H,), 7.15-7.25 (m, 3H), 7.34 (dm, 2H, J=8.6 Hz, unresolved).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.2, 15.0, 35.1, 37.2, 39.3, 60.8, 68.0, 80.1, 112.7, 115.6, 121.9 (overlapping signals), 129.2, 130.5, 138.0, 138.8, 147.8, 158.5, 172.5.

Example 31. 2-Ethoxy-3-{3-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid

Lithium hydroxide hydrate (0.175 g; 4.18 mmole) in water (5 ml) was slowly added to a solution of 2-ethoxy-3-{3-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester (1.66 g; 3.80 mmole) in tetrahydrofuran (17 ml) at 0° C. After stirring at room temperature for 2 hours tetrahydrofuran was removed by evaporation *in vacuo*. The water residue was washed with diethyl ether, the water phase was acidified with hydrochloric acid, and the product was extracted with ethyl acetate, washed with brine, dried (sodium sulfate), filtered and solvent was evaporated *in vacuo* to give 1.5 g of 2-ethoxy-3-{3-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}propanoic acid.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.13 (t, 3H, J=7 Hz), 2.91-2.98 (m, 1H), 3.03-3.09 (m, 3H), 3.09 (s, 3H), 3.33-3.41 (m, 1H), 3.56-3.64 (m, 1H), 4.03-4.08 (m, 1H), 4.13 (t, 2H, J=6.9 Hz), 6.75 (dd, 1H, J=8.3, 2.07 Hz), 6.81 (s, 1H), 6.84 (d, 1H, J=7.5 Hz), 7.14-7.23 (m ,3H), 7.31 (dm, 2H, J=8.56 Hz, unresolved), 10.91 (bs, 1OH).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 14.8, 35.0, 37.0, 38.8, 66.4, 67.9, 76.5, 112.7, 115.6, 121.78, 121.81, 129.1, 130.4, 137.8, 138.5, 147.7, 158.4, 176.7.

Example 32. 2-Ethoxy-3-{4-[3-(3-methanesulfonyloxyphenyl)propoxy]phenyl}propanoic acid ethyl ester

(a) 3-(3-Methanesulfonyloxyphenyl)propylmethanesulfonate

Methansulfonyl chloride (4.77 g; 41.8 mmole) in dichloromethane (20 ml) was slowly added to a solution of 3-(3-hydroxyphenyl)-1-propanol (3.03 g; 19.9 mmole) and triethylamine (6.04 g; 59.7 mmole) in dichloromethane at -20° C. The reaction mixture was allowed to reach room temperature and solid material was filtered off. The filtrate was washed with sodium bicarbonate solution (3 times) and brine, dried (magnesium sulfate) and the solvent was evaporated *in vacuo*. Purification by chromatography on silica gel using dichloromethane:methanol (gradient 0-8 % methanol) gave (4.22 g; yield 69 %) of the desired product.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 2.0 (m, 2H), 2.7 (t, 2H), 2.9 (s, 3H), 3.1 (s, 3H), 4.15 (t, 2H), 7.05-7.15 (m, 3H), 7.2-7.3 (m, 1H).
^{13}C-NMR (75 MHz; $CDCl_3$): δ 30.3, 31.2, 37.3, 37.4, 68.9, 119.8, 122.1, 127.6, 130.1, 143.0, 149.4.

(b) 2-Ethoxy-3-{4-[3-(3-methanesulfonyloxyphenyl)propoxy]phenyl}propanoic acid ethyl ester

2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester was alkylated with 3-(3-methanesulfonyloxyphenyl)propylmethanesulfonate in an alkylating reaction in the same way as 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate in example 1 (b) to give 2-ethoxy-3-{4-[3-(3-methanesulfonyloxyphenyl)propoxy]phenyl}propanoic acid ethyl ester.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.15 (t, 3H), 1.2 (t, 3H), 2.1 (qvint, 2H), 2.8 (t, 2H), 2.95 (d, 2H), 3.05 (s, 3H), 3.3-3.4 (m, 1H), 3.55-3.65 (m, 1H), 3.85-4.0 (m, 3H), 4.15 (q, 2H), -6.8 (d, 2H), 7.1-7.22 (m, 5H), 7.35 (t, 1H).

^{13}C-NMR (75 MHz; $CDCl_3$): δ 14.2, 15.1, 30.6, 31.9, 37.2, 38.4, 60.8, 66.2, 66.5, 80.4, 114.2, 119.5, 122.0, 127.6, 129.3, 129.9, 130.4, 144.2, 149.4, 157.6, 172.5.

Example 33. 2-Ethoxy-3-{4-[3-(3-methanesulfonyloxyphenyl)propoxy]phenyl}propanoic acid

2-Ethoxy-3-{4-[3-(3-methanesulfonyloxyphenyl)propoxy]phenyl}propanoic acid ethyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl]propanoic acid in example 2 to give 2-ethoxy-3-{4-[3-(3-methanesulfonyloxyphenyl)propoxy]phenyl}propanoic acid.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.15 (t, 3H), 2.1 (qvint, 2H), 2.85 (t, 2H), 2.9-3.07 (m, 2H), 3.1(s, 3H), 3.37-3.47 (m, 1H), 3.57-3.67 (m, 1H), 3.95 (t, 2H), 4.05 (m, 1H), 6.8 (d, 2H), 7.1-7.2 (m, 5H), 7.35 (t, 1H).

^{13}C-NMR (75 MHz; $CDCl_3$): δ 15.0, 30.6, 31.9, 37.3, 37.9, 66.5, 66.7, 79.8, 114.3, 119.5, 122.0, 127.6, 128.8, 129.9, 130.5, 144.2, 149.4, 157.8, 176.4.

Example 34. 3-{4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]phenyl}-2-methoxypropanoic acid methyl ester

(a) 3-(4-Benzyloxyphenyl)-2-methoxypropanoic acid methyl ester

Silver(I)oxide (2.43 g; 10.5 mmole), molecular sieves (4 Å, 2g) and methyl iodide (2.97 g; 20.9 mmole) were added to a solution of 3-(4-benzyloxyphenyl)-2-hydroxypropanoic acid methyl ester (2.0 g; 6.98 mmole) in dry dichloromethane (20 ml). The reaction mixture was refluxed for 72 hours, filtered through celite and washed with water. The organic phase

was dried with magnesium sulfate and evaporated *in vacuo* to give 1.93 g (yield 92 %) of an oil of 3-(4-benzyloxyphenyl)-2-methoxypropanoic acid methyl ester.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 2.90-3.01 (m, 2H), 3.35 (s, 3H), 3,71 (s, 3H), 3.91-3.96 (m, 1H), 5.04 (s, 2H), 6.90 (dm, 2H, J=8.6 Hz, unresolved), 7.13 (dm, 2H, J=8.6 Hz, unresolved), 7.29-7.35 (m, 1H), 7.35-7.40 (m, 2H), 7.40-7.43 (m, 2H).

(b) 3-(4-Hydroxyphenyl)-2-methoxypropanoic acid methyl ester

3-(4-Benzyloxyphenyl)-2-methoxypropanoic acid methyl ester (1.91 g; 6.36 mmole) was hydrogenated in methanol (30 ml) using Pd/C (5 %, wet, 0.9 g) as catalyst. The mixture was filtered through celite, dried (magnesium sulfate) and evaporated *in vacuo* to give 1.16 g (yield 87 %) of 3-(4-hydroxyphenyl)-2-methoxypropanoic acid methyl ester.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 2.93-3.03 (m, 2H), 3.38 (s, 3H), 3,75 (s, 3H), 3.94-3.99 (m, 1H), 5.02-5.12 (s br, 1 OH), 6.77 (dm, 2H, J=8.3 Hz, unresolved), 7.11 (dm, 2H, J=8.3 Hz, unresolved).

(c) 3-{4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]phenyl}-2-methoxypropanoic acid methyl ester

3-(4-Hydroxyphenyl)-2-methoxypropanoic acid methyl ester was alkylated with 2-(4-methanesulfonyloxyphenyl)ethylmethanesulfonate in an alkylating reaction in the same way as 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate in example 1 (b) to give 3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}-2-methoxypropanoic acid methyl ester.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 2.9-3.0 (m, 2H), 3.09 (t, 2H, J=6.7 Hz), 3.13 (s, 3H), 3.34 (s, 3H), 3.72 (s, 3H), 3.90-3-95 (m, 1H), 4.14 (t, 2H, J=6.7 Hz), 6.80 (dm, 2H, J=8.6 Hz,

unresolved), 7.11 (dm, 2H, J=8.6 Hz, unresolved), 7.22 (dm, 2H, J=8.6 Hz, unresolved), 7.33 (dm, 2H, J=8.6 Hz, unresolved).

Example 35. 3-{4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]phenyl}-2-methoxypropanoic acid .

3-{4-[2-(4-Methanesulfonyloxyphenyl)ethoxy]phenyl}-2-methoxypropanoic acid methyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}-ethoxy)phenyl]propanoic acid in example 2 to give 3-{4-[2-(4-methane-sulfonyloxyphenyl)ethoxy]phenyl}-2-methoxypropanoic acid

^{1}H-NMR (500 MHz; $CDCl_3$): δ 2.91-2.99 (m, 1H), 3.03-3.10 (m, 3H), 3.11 (s, 3H), 3.37 (s, 3H), 3.94-3.99 (m, 1H), 4.13 (t, 2H), 6.81 (dm, 2H, J=8.3 Hz, unresolved), 7.15 (dm, 2H, J=8.3 Hz, unresolved), 7.21 (dm, 2H, J=8.3 Hz, unresolved), 7.32 (dm, 2H, J=8.3 Hz, unresolved), 9.36 (bs, 1 H).
^{13}C-NMR (100 MHz; $CDCl_3$): δ 35.0, 37.1, 37.7, 58.5, 68.1, 81.2, 114.4, 121.9, 128.7, 130.3, 130.5, 137.9, 147.8, 157.5, 176.3.

Example 36. 2-Ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}butanoic acid ethyl ester

(a) 3-(4-Benzyloxyphenyl)-2-ethoxy-3-methylacrylic acid ethyl ester

LHMDS (11 ml, 11 mmole, 1 M in THF) was added to a solution of triethyl 2-ethoxyphosphonoacetate (2.95 g; 11 mmole) in dry tetrahydrofuran (30 ml) at -50° C under nitrogen atmosphere, the mixture was stirred for 1.5 hours and the temperature rised to 2°C. 1-(3-benzyloxy-phenyl)ethanone (2.3 g; 10 mmole) dissolved in tetrahydrofuran was slowly added and the resulting mixture was stirred overnight at room temperature. Saturated ammonium chloride solution (40 ml) was added and after 1 hour the phases were separated. The water phase was twice extracted with ethyl acetate, the organic phases were

combined and the solvent evaporated *in vacuo*. Purification twice by chromatography using ethyl acetate:heptane as eluent gave 0.6 g (yield 18 %) of 3-(4-benzyloxyphenyl)-2-ethoxy-3-methylacrylic acid ethyl ester as a mixture of Z and E isomers, which was used in the next step without further purification.

Major isomer

^{1}H-NMR (500 MHz; $CDCl_3$): δ 0.99 (t, 3H, J=7 Hz), 1.37 (t, 3H, J=7 Hz), 2.13 (s, 3H), 3.88 (q, 2H, J=7 Hz), 4.0 (q, 2H, J=7 Hz), 5.11 (s, 2H), 6.94 (dm, 2H, J=9 Hz, unresolved), 7.11 (dm, 2H, J=9 Hz, unresolved), 7.33-7.50 (m, 5H).

(b) 3-(4-Hydroxyphenyl)-2-ethoxybutanoic acid ethyl ester

3-(4-Benzyloxyphenyl)-2-ethoxy-3-methylacrylic acid ethyl ester (1.58 g; 4.64 mmole) was hydrogenated at atmospheric pressure in ethyl acetate (20 ml) using Pd/C (wet) as catalyst. After filtration on celite, the solvent was evaporated *in vacuo* to give (1.1 g; yield 94 %) of 3-(4-hydroxyphenyl)-2-ethoxybutanoic acid ethyl ester as a diastereomeric mixture.

Major isomer

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 1.25 (t, 3H, J=7 Hz), 1.32 (d, 3H, J=7 Hz),3.17 (qvint, 1H, J=7 Hz), 3.29-3.38 (m, 1H), 3.60-3.68 (m, 1H), 3.88-3.92 (m, 2H), 4.18 (q, 2H, J=7 Hz), 5.2 (bs, 1OH), 6.71-6.77 (m, 2H), 7.11-7.16 (m, 2H).

(c) 2-Ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}butanoic acid ethyl ester

3-(4-Hydroxyphenyl)-2-ethoxybutanoic acid ethyl ester was alkylated with 2-(4-methanesulfonyloxyphenyl)ethylmethanesulfonate in an alkylating reaction in the same way as 4-[2-(4-formylphenoxy)ethyl]phenylmethanesulfonate in example 1 (b) to

give 2-ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}butanoic acid ethyl ester as a diastereomeric mixture.

Major isomer

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.15 (t, 3H, J=7 Hz), 1.24 (t, 3H, J=7 Hz), 1.31 (d, 3H, J=7 Hz),2.99-3.20 (m, 6H), 3.28-3.35 (m, 1H), 3.58-3.65 (m, 1H), 3.88 (d, 1H, J=6.5 Hz), 4.14-4.20 (m, 4H), 6.83 (dm, 2H, J=8.5 Hz, unresolved), 7.18 (dm, 2H, J=8.5 Hz, unresolved), 7.25 (dm, 2H, J=8.5 Hz, unresolved),7.36 (dm, 2H, J=8.5 Hz, unresolved).

Example 37. 2-Ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}butanoic acid

2-Ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)-ethoxy]phenyl}butanoic acid ethyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}-ethoxy)phenyl]propanoic acid in example 2 to give 2-ethoxy-3-{4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl}butanoic acid as a diasteromeric mixture.

Major isomer

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.20 (t, 3H, J=8 Hz), 1.37 (d, 3H, J=7.2 Hz), 3.06-3.15 (m, 5H), 3.15-3.25 (m, 1H), 3.40-3.50 (m, 1H), 3.62-3.72 (m, 1H), 3.93 (d, 1H, J=5.6 Hz), 4.15 (t, 2H, J=6.8 Hz), 6.81 (dm, 2H, J=8,8 Hz, unresolved), 7.17 (dm, 2H, J=8,8 Hz, unresolved), 7.23 (dm, 2H, J=8,8 Hz, unresolved), 7.33 (dm, 2H, J=8,8 Hz, unresolved).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 15.0, 17.9, 35.1, 37.2, 41.7, 67.6, 68.1, 83.5, 114.2, 121.9, 129.2, 130.5, 133.5, 138.0, 147.8, 157.5, 175.4.

Example 38. 2-Ethoxy-3-(4-{2-[4-(2-propanesulfonyloxy)phenyl]-ethoxy}phenyl)propanoic acid ethyl ester

(a) 3-{4-[2-(4-Benzyloxyphenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester

Azodicarbonyl dipiperidine (7.5 g; 30 mmole) was added to 2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester (7 g; 30 mmole), 2-(4-benzyloxyphenyl)ethanol (6.8 g; 30 mmole) and triphenylphosphine (7.8 g; 30 mmole) dissolved i dichloromethane. After stirring at room temperature over night the solvent was evaporated *in vacuo* and diethyl ether was added. The solid material was filtered off after 1 hour and the filtrate was evaporated *in vacuo*. Purification by chromatography on silica gel using ethyl acetate:dichloromethane as eluent gave 10 g (yield 75 %) of 3-{4-[2-(4-benzyloxyphenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.15-1.30 (m, 6H), 2.95 (d, 2H), 3.05 (t, 2H), 3.3-3.42 (m, 1H), 3.58-3.7 (m, 1H), 4.0 (m, 1H), 4.05-4.25 (m, 4H), 5.05 (s, 2H), 6.85 (d, 2H), 6.95 (d, 2H), 7.1-7.25 (m, 4H), 7.3-7.5 (m, 5H).

^{13}C-NMR (75 MHz; $CDCl_3$): δ 14.3, 15.1, 35.0, 38.5, 60.8, 66.2, 68.9, 70.0, 80.5, 114.4, 114.9, 127.5, 128.0, 128.6, 129.3, 130.0, 130.4, 130.6, 137.1, 157.5, 157.6, 172.6.

b) 2-Ethoxy-3-{4-[2-(4-hydroxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester

3-{4-[2-(4-Benzyloxyphenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester (16 g; 35.6 mmole) was hydrogenated at atmospheric pressure in ethyl acetate (300 ml) using Pd/C (dry, 10 %) as catalyst. The mixture was filtered through celite and the solvent was evaporated *in vacuo* to give 11.2 g (yield 88 %) of 2-ethoxy-3-{4-[2-(4-hydroxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.1-1.30 (m, 6H), 2.9-3.05 (m, 4H), 3.3-3.45 (m, 1H), 3.55-3.70 (m, 1H), 4.0 (m, 1H), 4.1 (t, 2H), 4.02 (q, 2H), 6.5 (s br, 1 OH), 6.75-6.85 (m, 4H), 7.05-7.2 (m, 4H).

^{13}C-NMR (75 MHz; $CDCl_3$): δ 14.2, 15.0, 34.9, 38.4, 61.1, 66.3, 69.0, 80.4, 114.4, 115.5, 129.1, 129.8, 130.0, 130.4, 154.7, 157.6, 173.0.

(c) 2-Ethoxy-3-(4-{2-[4-(2-propanesulfonyloxy)phenyl]ethoxy}phenyl)propanoic acid ethyl ester

Triethylamine (0.64 g; 6.28 mmole) was slowly added to a solution of (1.5 g; 4.18 mmole) in dry dichloromethane (20 ml). After cooling to 0° C isopropylsulfonyl chloride (0.9 g; 6.28 mmole) was slowly added. The reaction mixture was stirred over night at room temperature, water was added and the crude product was extracted with dichloromethane. The organic phase was washed with hydrochloric acid 1M and sodium bicarbonate solution, dried (magnesium sulfate) and evaporated *in vacuo* to give 1.75 g (yield 90%) of 2-ethoxy-3-(4-{2-[4-(2-propanesulfonyloxy)phenyl]ethoxy}phenyl)propanoic acid ethyl ester.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.16 (t, 3H, J=7 Hz), 1.22 (t, 3H, J=7 Hz), 1.55 (d, 6H, J=6.7 Hz), 2.92-2.96 (m, 2H), 3.08 (t, 2H, J=7 Hz), 3.31-3.38 (m, 1H), 3.41-3.50 (m, 1H), 3.55-3.64 (m, 1H), 3.94-3.98 (m, 1H), 4.11-4-19 (m, 4H), 6.80 (dm, 2H, J=8.6 Hz, unresolved), 7.14 (dm, 2H, J=8.6 Hz, unresolved), 7.21 (dm, 2H, J=8.6 Hz, unresolved), 7.31 (dm, 2H, J=8.6 Hz, unresolved).

Example 39. 2-Ethoxy-3-(4-{2-[4-(2-propanesulfonyloxy)phenyl]ethoxy}phenyl)propanoic acid

2-Ethoxy-3-(4-{2-[4-(2-propanesulfonyloxy)phenyl]ethoxy}phenyl)propanoic acid ethyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl]propanoic acid in example 2 to give 2-ethoxy-3-(4-{2-[4-(2-propanesulfonyloxy)phenyl]ethoxy}phenyl)propanoic acid.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7.2 Hz), 1.54 (d, 6H, J=6.8 Hz), 2.91-2.98 (m, 1H), 3.03-3.1 (m, 3H), 3.38-3.52 (m, 2H), 3.55-3.65 (m, 1H), 4.01-4.06 (m, 1H), 4.14 (t, 2H, J=6.9 Hz), 6.81 (dm, 2H, J=8.6 Hz, unresolved), 7.15 (dm, 2H, J=8.6 Hz,

unresolved), 7.21 (dm, 2H, J=8.6 Hz, unresolved), 7.31 (dm, 2H, J=8.6 Hz, unresolved), 7.96 (bs, 1H).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 15.0, 16.7, 35.1, 37.8, 52.3, 66.8, 68.2, 79.7, 114.4, 121.9, 128.8, 130.4, 130.5, 137.4, 147.6, 157.5, 175.7.

Example 40. 2-Ethoxy-3-(4-{2-[4-(4-nitrobenzenesulfonyloxy)phenyl]ethoxy}phenyl)-propanoic acid ethyl ester

2-Ethoxy-3-{4-[2-(4-hydroxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester was esterified with 4-nitrobenzenesulfonyl chloride in the same way as 2-ethoxy-3-(4-{2-[4-(2-propanesulfonyloxy)phenyl]ethoxy}phenyl)propanoic acid ethyl ester in example 39 to give 2-ethoxy-3-(4-{2-[4-(4-nitrobenzenesulfonyloxy)phenyl]ethoxy}phenyl)propanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.16 (t, 3H, J=7 Hz), 1.23 (t, 3H, J=7 Hz), 2.92-2.97 (m, 2H), 3.05 (t, 3H, J=6.5 Hz), 3.30-3.39 (m, 1H), 3.54-3.65 (m, 1H), 3.93-3.99 (m, 1H), 4.12 (t, 2H, J=6.8 Hz), 4.16 (q, 2H, J=7 Hz), 6.77 (dm, 2H, J=8.8 Hz, unresolved), 6.93 (dm, 2H, J=8.8 Hz, unresolved), 7.14 (dm, 2H, J=8.8 Hz, unresolved), 7.23 (dm, 2H, J=8.8 Hz, unresolved), 8.03 (dm, 2H, J=8.8 Hz, unresolved), 8.36 (dm, 2H, J=8.8 Hz, unresolved).

Example 41. 2-Ethoxy-3-(4-{2-[4-(4-nitrobenzenesulfonyloxy)phenyl]ethoxy}phenyl)-propanoic acid

2-Ethoxy-3-(4-{2-[4-(4-nitrobenzenesulfonyloxy)phenyl]ethoxy}phenyl)propanoic acid ethyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid in example 2 to give 2-ethoxy-3-(4-{2-[4-(4-nitrobenzenesulfonyloxy)phenyl]ethoxy}phenyl)propanoic acid

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.16 (t, 3H, J=7 Hz), 2.91-3.01 (m, 1H), 3.01-3.08 (m, 2H), 3.37-3.45 (m, 1H), 3,58-3.66 (m, 1H), 4.0-4.06 (m, 1H) 4.08-4.14 (m, 2H), 6.78 (dm, 2H,

J=8.6 Hz, unresolved), 6.92 (dm, 2H, J=8.6 Hz, unresolved), 7.15 (dm, 2H, J=8.6 Hz, unresolved), 7.23 (dm, 2H, J=8.6 Hz, unresolved), 8.02 (dm, 2H, J=9.1 Hz, unresolved), 8.34 (dm, 2H, J=9.1 Hz, unresolved), 9.56 (bs, 1H).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 14.9, 35.0, 37.8, 66.6, 67.9, 79.6, 114.2, 115.3, 121.9, 124.2, 129.0, 129.8, 130.4, 138.3, 140.9, 147.7, 150.8, 157.4, 176.3.

Example 42. 3-{4-[2-(4-*Tert*-butylcarbamoyloxyphenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester

Tert-butyl isocyanate (0.14 g; 1.4 mmole) was slowly added to a solution of 2-ethoxy-3-{4-[2-(4-hydroxyphenyl)ethoxy]phenyl}propanoic acid ethyl ester (0.5 g; 1.4 mmole) in toluene (5 ml) and thereafter the reaction mixture was stirred over night. The crude mixture was purified by chromatography on silica gel using ethyl acetate:heptane (gradient 1.25-80 % ethyl acetate) as eluents to give 013 g (yield 20 %) of 3-{4-[2-(4-*tert*-butylcarbamoyloxyphenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.16 (t, 3H, J=7 Hz), 1.20 (t, 3H, J=7 Hz), 1.38 (s, 9H), 2.92-2.99 (m, 2H),3.05 (t, 2H, J=7 Hz), 3.31-3.38 (m, 1H), 3.55-3.64 (m, 1H), 3.94-3.99 (m, 1H), 4.0 (t, 2H, J=7 Hz), 4.16 (q, 2H, J=7 Hz),5.10 (bs, NH), 6.80 (dm, 2H, J=8.5 Hz, unresolved), 7.05 (dm, 2H, J=8.5 Hz, unresolved), 7.14 (dm, 2H, J=8.5 Hz, unresolved), 7.25 (dm, 2H, J=8.5 Hz, unresolved).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 14.9, 35.0, 37.8, 66.6, 67.9, 79.6, 114.2, 115.3, 121.9, 124.2, 129.0, 129.8, 130.4, 138.3, 140.9, 147.7, 150.8, 157.4, 176.3.

Example 43. 3-{4-[2-(4-*Tert*-butylcarbamoyloxyphenyl)ethoxy]phenyl}-2-ethoxypropanoic acid

3-{4-[2-(4-*Tert*-butylcarbamoyloxyphenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-

phenyl}-ethoxy)phenyl]propanoic acid in example 2 to give 3-{4-[2-(4-*tert*-butylcarbamoyloxyphenyl)ethoxy]phenyl}-2-ethoxypropanoic acid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 1.32 (s, 9H), 2.90-2.97 (m, 2H), 3.01 (t, 2H, J=7 Hz), 3.40-3.50 (m, 1H), 3.53-3.65 (m, 1H), 4.03 (m, 1H), 4.10 (t, 2H; J=7 Hz), 6.79 (dm, 2H, J=8.5 Hz, unresolved), 6.81 (dm, 2H, J=8.5 Hz, unresolved), 7.11-7.16 (m, 4H)

Example 44. 2-Phenylsulfanyl-3-{4-[2-(4-phenylsulfanylphenyl)ethoxy]phenyl}propanoic acid ethyl ester

(a) 3-(4-Hydroxyphenyl)-2-phenylsulfanylpropanoic acid ethyl ester

Tetrabutylammonium fluoride trihydrate (19.9 g; 63 mmole) was added to a solution of in tetrahydrofuran (23.9 g; 57.4 mmole) (200 ml). After stirring at room temperature for 2 hours the solvent was evaporated *in vacuo*, ethyl acetate and hydrochloric acid (1 M) were added, the phases were seperated and the organic phase was washed with water and dried (sodium sulfate). Purification by chromatography on silica gel using heptan/ethyl acetate as eluent gave 16.4 g (yield 94 %) of 3-(4-hydroxyphenyl)-2-phenylsulfanyl-propanoic acid ethyl ester.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.44 (m, 2H), 7.28 (m, 3H), 7.03 (d, J=8.4 Hz, 2H), 6.70 (d, 8.4 Hz, 2H), 4.02 (m, 2H), 3.86 (dd, J=9.5 and 6.0 Hz, 1H), 3.11 (dd, J=14.0 and 9.5 Hz, 1H), 3.00 (dd, J=14.0 and 6.0 Hz, 1H), 1.07 (t, J=7.1 Hz, 3H).

(b) 2-Phenylsulfanyl-3-{4-[2-(4-phenylsulfanylphenyl)ethoxy]phenyl}propanoic acid ethyl ester

2-(4-Phenylsulfanylphenyl)ethanol (0.662 g; 2.88 mmole), azodicarbonyl dipiperidine (0.835 g; 3.31 mmole) and triphenylphosphine (0.868 g; 3.31 mmole) were dissolved in

dichloromethane (15 ml) at room temperature. After stirring for 10 minutes 3-(4-hydroxyphenyl)-2-phenylsulfanylpropanoic acid ethyl ester (1 g; 3.31 mmole) dissolved in dichloromethane (10 ml) was added. After stirring at room temperature for 12 hours more of azodicarbonyl dipiperidine (0.2 g) and more of triphenylphosphine (0.2 g) were added. Solid material was filtered off after 6 more hours. Purification by chromatography on silica gel using heptan:ethyl acetate (8:1) as eluent gave 1.32 g (yield 70%) of 2-phenylsulfanyl-3-{4-[2-(4-phenylsulfanylphenyl)ethoxy]phenyl}propanoic acid ethyl ester as a pale yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.33 (d, J=8.2 Hz, 2H), 7.15 (d, J=8.6 Hz, 2H), 7.12 (d, J=8.2 Hz, 2H), 6.82 (d, J=8.6 Hz, 2H), 4.17 (m, 4H), 3.97 (dd, J=7.1 and 6.1 Hz, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 3.23 (s, 3H), 3.11 (t, J=7.1 Hz, 2H), 2.95 (m, 2H), 2.52 (sept, J=6.7 Hz, 1H), 1.23 (t, J=7.1 Hz, 3H), 1.16 (t, J=6.9 Hz, 3H), 1.03 (d, J=6.7 Hz, 6H).

Example 45. 2-(Phenylsulfanyl)-3-[4-(2-{4-phenylsulfanylphenyl}ethoxy)-phenyl]propanoic acid

Lithium hydroxide hydrate (4 mg; 0.096 mmole) dissolved in 0.3 ml water was added to a solution of (25 mg; 0.048 mmole) 2-phenylsulfanyl-3-{4-[2-(4-phenylsulfanylphenyl)-ethoxy]phenyl}propanoic acid ethyl ester in 1 ml tetrahydrofuran. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was acidified with 6 M hydrochloric acid, 2 ml water was added and the product was extracted with ethyl acetate, dried (sodium sulfate) and solvent was evaporated *in vacuo*. Purification by chromatography on silica gel using heptan:ethyl acetate:acetic acid (10:10:1) as eluent gave of 5 mg (yield 21 %) 2-(phenylsulfanyl)-3-[4-(2-{4-phenylsulfanylphenyl}ethoxy)-phenyl]propanoic acid.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (m, 2H), 7.28 (m, 10H), 7.20 (d, J=8.2 Hz, 2H), 7.10 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.6 Hz, 2H), 4.11 (t, J=7.0 Hz, 2H), 3.82 (dd, J=8.7 and 6.6

Hz, 1H), 3.12 (dd, J=14.1 and 8.7 Hz, 1H), 3.04 (t, J=7.0 Hz, 2H), 2.99 (dd, J=14.1 and 6.6 Hz, 1H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 175.8, 157.7, 137.6, 136.2, 133.3, 133.0, 132.9, 131.6, 130.6, 130.1, 129.9, 129.6, 129.1, 129.0, 128.2, 126.8, 114.6, 68.4, 52.3,37.0, 35.4.

Example 46. 3-{4-[2-(4-Methanesulfonylphenyl)ethoxy]phenyl}-2-phenylsulfanylpropanoic acid ethyl ester

Azodicarbonyl dipiperidine (0.5 g; 1.98 mmole) and triphenylphosphine (0.52 g; 1.98 mmole) were added to a solution of 2-(4-methylsulfonylphenyl)ethanol (0.4 g; 1.98 mmole) and 3-(4-hydroxyphenyl)-2-phenylsulfanylpropanoic acid ethyl ester (0.5 g; 1.65 mmole) in dichloromethane (20 ml) at room temperature. After stirring at room temperature for 24 hours more of azodicarbonyl dipiperidine (0.1 g) and more of triphenylphosphine (0.1 g) were added. Solid material was filtered off after 30 hours. Purification by chromatography on silica gel using heptan:ethyl acetate (gradient 3:1 to 1:1) as eluent gave 0.585 g (yield 73 %) of 3-{4-[2-(4-methanesulfonyl-phenyl)ethoxy]phenyl}-2-phenylsulfanylpropanoic acid ethyl ester as a colourless oil that crystallize on standing.

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.9-7.2 (m, 9H), 7.1 (d, 2H), 6.8 (d, 2H), 4.2 (m, 2H), 4.0 (m, 2H), 3.8 (m, 1H), 3.2-2.9 (m, 4H), 3.0 (s, 3H), 1.1 (t, 3H).

Example 47. 3-{4-[2-(4-Methanesulfonylphenyl)ethoxy]phenyl}-2-phenylsulfanylpropanoic acid

Lithium hydroxide hydrate (4.3 mg; 0.103 mmole) dissolved in 0.3 ml water was added to a solution of 3-{4-[2-(4-methanesulfonylphenyl)ethoxy]phenyl}-2-phenylsulfanyl-propanoic acid ethyl ester (25 mg; 0.052 mmole) in 1 ml tetrahydrofuran. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was acidified

with hydrochloric acid (6 M), 2 ml water (2 ml) was added and the product was extracted with ethyl acetate, dried (sodium sulfate) and solvent was evaporated *in vacuo*. Purification by chromatography on silica gel using heptan:ethyl acetate:acetic acid (10:10:1) as eluent gave 5 mg (yield 21 %) of the desired product.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.85 (d, J=8.3 Hz, 2H),7.45 (d, J=8.3 Hz, 2H), 7.40 (m, 2H), 7.25 (m, 3H), 7.09 (d, J=8.5 Hz, 2H), 6.76 (d, J=8.5 Hz, 2H), 4.16 (t, J=6.4 Hz, 2H), 3.82 (m, 1H), 3.13 (t, J=6.4 Hz, 2H), 3.10 (m, 1H), 3.02 (s, 3H), 2.97 (m, 1H).
^{13}C NMR (150 MHz; $CDCl_3$): δ 175.5,157.5,145.2, 138.7, 133.1, 132.8, 130.2, 130.0, 129.1, 128.1, 127.5, 114.6, 67.6, 52.4, 44.5, 37.0, 35.7.

Example 48. 3-{4-[2-(4-Cyanophenyl)ethoxy]phenyl}-2-phenylsulfanylpropionic acid ethyl ester

3-(4-Hydroxyphenyl)-2-phenylsulfanylpropanoic acid ethyl ester was reacted with p-cyanophenyl ethanol in a Mitsunobu reaction in the same way as in 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester in example 15 (d) to give 3-{4-[2-(4-cyanophenyl)ethoxy]phenyl}-2-phenylsulfanylpropionic acid ethyl ester.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 1.08 (t, 3H), 2.99 (dd, 1H), 3.1-3.2 (m, 3H), 3.84 (dd, 1H), 3.97-4.07 (m, 2H), 4.16 (t, 2H), 6.77 (dm, 2H, J=8.7 Hz, unresolved), 7.10 (dm, 2H, J=8.4 Hz, unresolved), 7.26-7.31 (m, 3H), 7.39 (dm, 2H, J=8.0 Hz, unresolved), 7.41-7.45 (m, 2H), 7.60 (dm, 2H, J=8.4 Hz, unresolved).

Example 49. 3-{4-[2-(4-Cyanophenyl)ethoxy]phenyl}-2-phenylsulfanylpropanoic acid

3-{4-[2-(4-Cyanophenyl)ethoxy]phenyl}-2-phenylsulfanylpropionic acid ethyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-

phenyl}ethoxy)phenyl]propanoic acid in example 2 to give 3-{4-[2-(4-cyanophenyl)-ethoxy]phenyl}-2-phenylsulfanylpropanoic acid.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 2.96-3.2 (m, 1H), 3.07-3.14 (m, 3H), 3.77-3.83 (m, 1H), 4.14 (t, 2H, J=6.5 Hz), 6.78 (dm, 2H, J=8.8 Hz, unresolved), 7.10 (dm, 2H, J=8.8 Hz, unresolved), 7.23-7.28 (m, 3H), 7.35 (dm, 2H, J=8.3 Hz, unresolved), 7.38-7.43 (m, 2H), 7.56 (dm, 2H, J=8.3 Hz, unresolved).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 35.7, 36.7, 52.1, 67.5, 110.3, 114.5, 118.8, 128.2, 129.0, 129.70, 129.73, 130.1, 132.1, 132.7, 133.0, 144.1, 157.4, 177.3.

Example 50. 2-Ethoxy-3-{4-[2-(4-methylsulfanylphenyl)ethoxy]phenyl}propanoic acid ethyl ester

2-(4-Methylsulfanylphenyl)ethanol was reacted with 2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester in a Mitsunobu reaction in the same way as in 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester in example 15 (d) to give 2-ethoxy-3-{4-[2-(4-methylsulfanylphenyl)ethoxy]-phenyl}propanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.17 (t, 3H), 1.24 (t, 3H), 2.49 (s, 3H), 2.94-2.97 (m, 2H), 3.05 (t, 2H), 3.32-3.40 (m, 1H), 3.57-3.65 (m, 1H), 3.95-3.99 (m, 1H), 4.11-4.21 (t+q, 4H), 6.82 (d, 2H), 7.15 (d, 2H), 7.2-7.28 (m, 4H).

Example 51. 2-Ethoxy-3-{4-[2-(4-methylsulfanylphenyl)ethoxy]phenyl}propanoic acid

2-Ethoxy-3-{4-[2-(4-methylsulfanylphenyl)ethoxy]phenyl}propanoic acid ethyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid in example 2 using dioxane instead of THF to give 2-ethoxy-3-{4-[2-(4-methylsulfanylphenyl)ethoxy]phenyl}-propanoic acid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.19 (t, 3H), 2.49 (s, 3H), 2.92-2.99 (dd, 1H) 3.03-3.11 (dd+t, 3H), 3.41-3.50 (m, 1H), 3.59-3.65 (m, 1H), 4.04-4.07 (dd, 1H), 4.14 (t, 2H), 6.83 (d, 2H), 7.16 (d, 2H), 7.20-7.28 (m, 4H).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 16.1, 17.3, 36.4, 38.8, 68.0, 69.6, 80.9, 115.5, 128.2, 129.7, 130.6, 131.6, 136.4, 137.3, 158.8, 175.9.

Example 52. 2-Ethoxy-3-{4-[2-(4-methanesulfonylphenyl)ethoxy]phenyl}propanoic acid ethyl ester

3-Chloroperoxybenzoic acid (0.73 g; 4.20 mmole) was added to a solution of 2-ethoxy-3-{4-[2-(4-methylsulfanylphenyl)ethoxy]phenyl}propanoic acid ethyl ester (0.65 g; 1.68 mmole) in dichloromethane (20 ml) at 0°C. After stirring at room temperature for 3 hours, water (20 ml) was added. The product was extracted with ethyl acetate (20 ml), washed with saturated sodium bicarbonate, dried (sodium sulfate) filtered and the solvent was evaporated *in vacuo*. Purifiaction by chromatography on silica gel using heptan:ethyl acetate (1:1) as eluent gave (0.399 g; yield 56 %) of 2-ethoxy-3-{4-[2-(4-methanesulfonylphenyl)ethoxy]phenyl}propanoic acid ethyl ester slightly polluted by 3-chloroperoxybenzoic acid.

^{1}H NMR (600 MHz; $CDCl_3$): δ 7.89 (d, J=8.3 Hz, 2H), 7.49 (d, J=8.3 Hz, 2H), 7.15 (d, J=8.7 Hz, 2H), 6.80 (d, J=8.7 Hz, 2H), 4.19 (t, J=6.5 Hz, 2H), 4.17 (m, 2H), 3.96 (dd, J=7.4 and 5.8 Hz, 1H), 3.60 (m, 1H), 3.34 (m, 1H), 3.17 (t, J=6.5, 2H), 3.05 (s, 3H), 2.95 (m, 2H), 1.23 (t, J=7.1, 3H), 1.16 (t, J=7.0 Hz, 3H).

Example 53. 2-Ethoxy-3-{4-[2-(4-methanesulfonylphenyl)ethoxy]phenyl}propanoic acid

Lithium hydroxide hydrate (57 mg; 1.37 mmole) dissolved in 2 ml water was added to a solution of 2-ethoxy-3-{4-[2-(4-methanesulfonylphenyl)ethoxy]phenyl}propanoic acid ethyl ester (384 mg; 0.91 mmole) in 6 ml tetrahydrofuran. After stirring at room

temperature for 2 hours 30 mg more of lithium hydroxide hydrate dissolved in 1 ml of water was added. The reaction mixture was stirred at room temperature for 4 more hours. The reaction mixture was acidified with hydrochloric acid (2 M) to pH 4. Tetrahydrofuran was evaporated *in vacuo*, 5 ml water was added and the product was extracted with 10 ml ethyl acetate. The organic phase was washed with water, dried (sodium sulfate) and solvent was evaporated *in vacuo*. Purification by chromatography on silica gel using heptan:ethyl acetate:acetic acid (10:10:1) as eluent gave 0.307 g (yield 86 %) of the desired product as a pale yellow oil that crystallizes when vacuum dried.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.16 (t, 3H, J=7 Hz), 2.87-3.10 (m, 5H), 3.16 (t, 2H, J=6.4 Hz), 3.36-3.48 (m, 1H), 3.53-3.66 (m, 1H), 3.98-4.07 (m, 1H), 4.18 (t, 2H, J=6.4 Hz), 6.75-6.85 (m, 2H), 7.10-7.20 (m, 2H), 7.46-7.55 (m, 2H), 7.86-7.96 (m, 2H).
^{13}C-NMR (75 MHz; $CDCl_3$): δ 11.4, 35.7, 37.8, 44.6, 66.7, 67.6, 79.8, 114.4, 127.5, 129.0, 129.1, 130.0, 130.6, 145.2, 157.4, 175.4.

Example 54. 3-{4-[2-(4-Cyanophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester

3-{4-[2-(4-Cyanophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester was synthesized in the same way as 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester in example 15 (d) using 2-ethoxy-3-(4-hydroxyphenyl) propanoic acid ethyl ester (6.62 g; 27.78 mmole) and p-cyanophenethyl alcohol (2.73 g; 18.52 mmole). The reaction was interrupted after 2 hours. Purification by chromatography on silica gel using first dichloromethane and then petroleum ether:diethyl ether as eluents gave a mixture of product and starting material which was dissolved in ethyl acetate and washed with sodium hydroxide (1 N). The organic phase was washed with water, dried (sodium sulfate), filtered and solvent was evaporated to give 4.23 g (yield 62 %). of 3-{4-[2-(4-cyanophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.16 (t, 3H, J=7 Hz), 1.23 (t, 3H, J=7 Hz), 2.93-2.97 (m, 2H), 3.14 (t, 2H, J=6.4 Hz), 3.3-3.4 (m, 1H), 3.56-3.65 (m, 3H), 3.94-3.99 (m, 1H), 4.14-

4.26 (m, 4H), 6.8 (dm, 2H, J=8.6 Hz, unresolved), 7.15 (dm, 2H, J=8.6 Hz, unresolved), 7.4 (dm, 2H, J=8.3 Hz, unresolved), 7.60 (dm, 2H, J=8.3 Hz, unresolved).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.1, 15.0, 35.8, 38.4, 60.7, 66.1, 67.5, 80.2, 110.3, 114.2, 118.8, 129.66, 129.74, 130.4, 132.1, 144.2, 157.2, 172.4.

Example 55. 3-{4-[2-(4-Methylsulfanylphenyl)ethoxy]phenyl}-2-phenoxypropanoic acid methyl ester

(a) 3-(4-Benzyloxyphenyl)-2-phenoxypropanoic acid methyl ester

3-(4-Benzyloxyphenyl)-2-hydroxypropanoic acid methyl ester was reacted with phenol in a Mitsunobu reaction in the same way as in 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester in example 15 (d) to give 3-(4-benzyloxyphenyl)-2-phenoxypropanoic acid methyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.21 (m, 2H), 3.70 (s, 3H), 4.80 (dd, 1H, J=5.4 Hz; 7.3 Hz), 5.31 (s, 2H), 6.86 (dm, 2H, J=7.8 Hz, unresolved), 6.96 (m, 3H), 7.25 (m, 4H), 7.38 (m, 5H).

(b) 3-(4-Hydroxyphenyl)-2-phenoxypropanoic acid methyl ester

3-(4-Benzyloxyphenyl)-2-phenoxypropanoic acid methyl ester (0.47 g; 1.3 mmole) was hydrogenated in ethyl acetate (20 ml) using Pd/C (18 mg; 5 %) as catalyst at atmospheric pressure and room temperature for 23 hours. As the reaction was very slow, the catalyst was changed to palladium hydroxide, ethanol (95%, 10 ml) was added and the pressure was raised to 4 bar. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to give 0.34 g (yield 95 %) of 3-(4-hydroxyphenyl)-2-phenoxypropanoic acid methyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.19 (m, 2H), 3.72 (s, 3H), 4.79 (dd, 1H, J=5.4 Hz; 7.3 Hz), 6.76 (dm, 2H, J=8.3 Hz, unresolved), 6.85 (dd, 2H, J=1.0 Hz; 8.8 Hz), 6.97 (m, 1H), 7.16 (dm, 2H, J=8.8 Hz, unresolved), 7.27 (m, 2H).

(c) 3-{4-[2-(4-Methylsulfanylphenyl)ethoxy]phenyl}-2-phenoxypropanoic acid methyl ester

3-(4-Hydroxyphenyl)-2-phenoxypropanoic acid methyl ester was reacted with 2-(4-methylsulfanylphenyl)ethanol in a Mitsunobu reaction in the same way as in 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester in example 15 (d) to give 3-{4-[2-(4-methylsulfanylphenyl)ethoxy]phenyl}-2-phenoxy-propanoic acid methyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.50 (s, 3H), 3.07 (t, 2H, J=7.0 Hz), 3.22 (m, 2H), 3.74 (s, 3H), 4.16 (t, 2H, J=7.0 Hz), 4.81 (dd, 1H, J=5.2 Hz; 7.5 Hz), 6.87 (m, 4H), 6.99 (t, 1H, J=7.5 Hz), 7.26 (m, 8H).

Example 56. 3-{4-[2-(4-Methylsulfanylphenyl)ethoxy]phenyl}-2-phenoxypropanoic acid

3-{4-[2-(4-Methylsulfanylphenyl)ethoxy]phenyl}-2-phenoxypropanoic acid methyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl]propanoic acid in example 2 to give 3-{4-[2-(4-methylsulfanyl-phenyl)ethoxy]phenyl}-2-phenoxypropanoic acid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.50 (s, 3H), 3.07 (t, 2H, J=7.3 Hz), 3.26 (d, 2H, J=6.4 Hz), 4.15 (t, 2H, J=6.8 Hz), 4.84 (t, 1H, J=5.4 Hz), 6.88 (m, 4H), 7.05 (dt, 1H, J=1.0 Hz; 7.3 Hz), 7.27 (m, 8H).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 17.3, 36.3, 39.1, 69.7, 78.7, 115.7, 116.5, 123.2, 128.2, 129.3, 130.6, 130.8, 131.7, 136.4, 137.4, 158.6, 160.0, 177.9.

Example 57. 2-Ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester

(a) N-[4-(2-hydroxyethyl)phenyl]isobutyramide

2-Methylpropanic acid anhydride (24.15 g; 153 mmole) was slowly added to a warm solution of 4-aminophenethyl alcohol (21 g; 153 mmole) in acetone (200 ml). After reflux for 1 hour more 2-methylpropanic acid anhydride (1 g) was added. After 1,5 hours the solvent was evaporated *in vacuo* and the solid residue was crystallized in dichloromethane/heptane to give of white crystals of 30.7 g (yield 97 %) N-[4-(2-hydroxyethyl)phenyl]isobutyramide.

^{1}H-NMR (400 MHz; Acetone-d_6): d 1.20 (d, 6H, J=6.7 Hz), 2.54-2.64 (m, 1H), 2.80 (t, 2H, J=7 Hz), 3.40 (t, 1 OH, J=5.6 Hz), 3.75-3.80 (m, 2H), 7.13 (dm, 2H, J=8.5 Hz, unresolved), 7.53 (dm, 2H, J=8.5 Hz, unresolved), 8.77 (s br, 1 NH).

(b) 2-Ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester

2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester (0.71 g; 2.97 mmole) dissolved in dichloromethane (5 ml) was added to a mixture of N-[4-(2-hydroxyethyl)phenyl]-isobutyramide (0.5 g; 2.47 mmole), azodicarbonyl dipiperidine (0.75 g; 2.97 mmole) and triphenylphosphine (0.78 g; 2.97 mmole) in dichloromethane (15 ml). After stirring at room temperature over night the reaction mixture was filtered, solvent was evaporated *in vacuo* and purification by chromatography on silica gel using heptan:ethyl acetate (gradient 3:1 to 1:1) as eluent gave of 0.69 g (yield 65%) of 2-ethoxy-3-{4-[2-(4-isobutyrylamino-phenyl)ethoxy]phenyl}propanoic acid ethyl ester.

^{1}H NMR (500 MHz; $CDCl_3$): δ 7.47 (d, J=8.2 Hz, 2H), 7.22 (d, J=8.2 Hz, 2H), 7.13 (d, J=8.6 Hz, 2H), 6.80 (d, J=8.6 Hz, 2H), 4.16 (q, J=7.1 Hz, 2H),4.11 (t, J=7.1 Hz, 2H), 3.96 (dd, J=7.4 and 6.0 Hz, 1H), 3.59 (m, 1H), 3.34 (m, 1H), 3.04 (t, J=7.1 Hz, 2H), 2.94 (m,

2H), 2.50 (sept, J=6.9 Hz, 1H), 1.25 (d, J=6.9 Hz, 6H), 1.22 (t, J=7.1 Hz, 3H), 1.16 (t, J=7.0 Hz, 3H).

Example 58. 2-Ethoxy-3-[4-(2-{4-isobutyrylaminophenyl}ethoxy)phenyl]propanoic acid

2-Ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl]propanoic acid in example 2 to give 2-ethoxy-3-[4-(2-{4-isobutyrylaminophenyl}ethoxy)phenyl]propanoic acid (yield 97 %).

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.46 (d, 8.3 Hz, 2H), 7.37 (s, NH, 1H), 7.20 (d, J=8.3 Hz, 2H), 7.13 (d, J=8.5 Hz, 2H), 6.79 (d, J=8.5 Hz, 2H), 4.11 (m, 2H), 4.02 (dd, J=7.6 and 4.6 Hz, 1H), 3.60 (dq, J=9.3 and 7.0 Hz, 1H), 3.40 (dq, J=9.3 and 7.0 Hz, 1H), 3.02 (m, 3H), 2.93 (dd, J=14.1 and 7.7 Hz, 1H), 2.50 (m, 1H), 1.23 (d, J=6.9 Hz, 6H), 1.14 (t, J=7.0 Hz, 3H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 175.5, 175.3, 157.7, 136.4, 134.2, 130.5, 129.5, 128.8, 120.1, 114.4, 79.8, 68.6, 66.7, 37.9, 36.6, 35.2, 19.6, 15.0

Example 59. (S)-2-Ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester

(a) 3-(4-Benzyloxyphenyl)-2-ethoxypropanoic acid ethyl ester

3-(4-Benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester (0.5 g; 1.5 mmole) was hydrogenated at atmospheric pressure using 5 % rhodium on charcoal as catalyst (50 mg) in methanol (20 ml). The crude product was purified by chromatography using heptane:ethyl acetate (5:1) as eluent to give 50 mg (yield 10%) of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid ethyl ester.

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.47-7.30 (m, 5H), 7.17 (d, J=8.8, 2H), 6.91 (d, J=8.8 Hz, 2H), 5.06 (s, 2H), 4.17 (q, J=7.2 Hz, 2H), 3.98 (t, J=6.6 Hz, 1H), 3.61 (dq, J=8.9 and 6.8 Hz, 1H), 3.36 (dq, J=8.9 and 6.8 Hz, 1H), 2.97 (d, J=6.6 Hz, 2H), 1.22 (t, J=7.2 Hz, 3H), 1.18 (t, J=6.8 Hz, 3H).

^{13}C NMR (75 MHz; $CDCl_3$): δ/ppm 172.6, 157.6, 137.1, 130.4, 129.5, 128.6, 127.9, 127.5, 114.6, 80.4, 70.0, 66.2, 60.8, 38.5, 15.1, 14.2.

(b) 3-(4-Benzyloxyphenyl)-2-ethoxypropanoic acid

Lithium hydroxide hydrate (7.4 g; 177 mmole) dissolved in water (150 ml) was added to a solution of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid ethyl ester (23.25 g; 70.8 mmole) in dioxane (150 ml). After stirring at room temperature over night dioxane was evaporated *in vacuo*, water was added and the mixture was washed with ethyl acetate. The water phase was acidified with hydrochloric acid (1 N) and the crude product was extracted with ethyl acetate, washed with water and brine, dried and solvent was evaporated *in vacuo* to give 21.1 g (yield 99,2 %) of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid.

^{1}H NMR (300 MHz; $CDCl_3$): δ 1.15 (t, 3H), 2.9-3.1 (m, 2H), 3.35-3.45 (m, 1H), 3.6-3.7 (m, 1H), 3.95-3.41 (m, 1H), 5.05 (s, 2H), 6.95 (d, 2H), 7.2 (d, 2H), 7.25-7.5 (m, 5H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 15.0, 38.1, 66.6, 70.0., 79.9, 114.7, 127.5, 128.0, 128.6, 129.3, 130.5, 137.1, 157.7, 176.3.

(c) 3-(4-Benzyloxyphenyl)-(S)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide and 3-(4-benzyloxyphenyl)-(R)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide

EDC (2.03 g; 10.61 mmole), diisopropylethylamin (1.84 ml; 10.61 mmole) and HOBtxH2O (1.43 g; 10.61 mmole) were added to a solution of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid (2.92 g; 9.74 mmole) in 30 ml dry dichloromethane on an ice bath. After 30 minutes the ice bath was removed and R(-)-phenylglycine and (1.46 g; 10.61

mmole) was added. After stirring at room temperature over night 100 ml ethyl acetate was added and the solution was washed with potassium hydrogensulfate (1 M), saturated sodium bicarbonatesolution, sodium carbonatesolution and water. The organic phase was dried (sodium sulfate), filtered and solvent was evaporated *in vacuo*. The crude product was purified by chromatography on silica gel using ethyl acetate:heptan to give 1.5 g (yield 37 %) of 3-(4-benzyloxyphenyl)-(S)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide and 1.25 g (yield 31 %) of 3-(4-benzyloxyphenyl)-(R)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide.

3-(4-Benzyloxyphenyl)-(S)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.43-7.27 (m, 8H), 7.22 (d, J=8.3 Hz, 4H), 7.13 (d, NH, J=7.8 Hz, 1H), 6.96 (d, J=8.3 Hz, 1H), 5.08 (s, 2H), 5.01 (m, 1H), 3.99 (dd, J=6.8 and 3.9 Hz, 1H), 3.69 (m, 2H), 3.50 (q, J=6.8 Hz, 2H), 3.15 (dd, J=14.2 and 3.9 Hz, 1H), 2.97 (dd, J=14.2 and 6.8 Hz, 1H), 2.94 (m, OH, 1H), 1.16 (t, J=6.8 Hz, 3H).
^{13}C NMR (100 MHz; $CDCl_3$): δ 172.3, 157.5, 138.9, 137.0, 130.7, 129.4, 128.6, 128.4, 127.7, 127.6, 127.3, 126.5, 114.4, 81.0, 69.8, 66.3, 66.0, 55.3, 37.8, 15.1.

3-(4-Benzyloxyphenyl)-(R)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.49-7.20 (m, 9H), 7.13 (d, J=8.8 Hz, 4H), 7.08 (d, J=8.3 Hz, 4H), 6.86 (d, J=8.8 Hz, 1H), 5.04 (s, 2H), 5.01 (m, 1H), 4.01 (dd, J=6.8 and 3.9 Hz, 1H), 3.83 (m, 2H), 3.57 (m, 2H), 3.16 (m, OH, 1H), 3.09 (dd, J=14.2 and 3.9 Hz, 1H), 2.91 (dd, J=14.2 and 6.8 Hz, 1H), 1.21 (t, J=6.8 Hz, 3H).
^{13}C NMR (100 MHz; $CDCl_3$): δ 172.3, 157.4, 138.6, 137.0, 130.6, 129.3, 128.5, 128.4, 127.8, 127.4, 127.3, 126.4, 114.4, 81.1, 69.8, 66.4, 66.1, 54.9, 37.5, 15.1.

(d) 3-(4-Benzyloxyphenyl)-2-(S)-ethoxypropanoic acid

3-(4-Benzyloxyphenyl)-(S)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide (8.9 g; 21.22 mmole) was hydrolyzed with concentrated sulfuric acid (27 ml) in water (104 ml) and dioxane (104) at 90° C for 5 hours. The reaction mixture was poured onto water

(220 ml) and extracted with ethyl acetate. The organic phase was washed with brine, dried (sodum sulfate) and solvent was evaporated *in vacuo* to give 6.8 g of a mixture of 3-(4-benzyloxyphenyl)-2-(S)-ethoxypropanoic acid and debenzylated 3-(4-benzyloxyphenyl)-2-(S)-ethoxypropanoic acid which was used without further purification.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.47-7.30 (m, 5H), 7.19 (d, J=8.8, 2H), 6.93 (d, J=8.8 Hz, 2H), 5.10 (s, 2H), 4.06 (dd, J=7.8 and 4.4 Hz, 1H), 3.64 (dq, J=9.8 and 6.8 Hz, 1H), 3.44 (dq, J=9.8 and 6.8 Hz, 1H), 3.09 (dd, J=14.2 and 4.4 Hz, 1H), 2.98 (dd, J=14.2 and 7.8 Hz, 1H), 1.19 (t, J=6.8 Hz, 3H).

(e) 3-(4-Benzyloxyphenyl)-2-(S)-ethoxypropanoic acid

Hydrogen chloride (g) was bubbled through a solution of 3-(4-benzyloxyphenyl)-2-(S)-ethoxypropanoic acid (6.85 g; 22.8 mmole) in ethanol (400 ml). Thionyl chloride (2 ml; 27.4 mmole) was slowly added and the reaction mixture was refluxed for 2 hours. Solvent was evaporated to give 8 g of a mixture of starting material and (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester which was used without further purification.

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.47-7.30 (m, 5H), 7.17 (d, J=8.8, 2H), 6.91 (d, J=8.8 Hz, 2H), 5.06 (s, 2H), 4.17 (q, J=7.2 Hz, 2H), 3.98 (t, J=6.6 Hz, 1H), 3.61 (dq, J=8.9 and 6.8 Hz, 1H), 3.36 (dq, J=8.9 and 6.8 Hz, 1H), 2.97 (d, J=6.6 Hz, 2H), 1.22 (t, J=7.2 Hz, 3H), 1.18 (t, J=6.8 Hz, 3H).

^{13}C NMR (75 MHz): δ 172.6, 157.6, 137.1, 130.4, 129.5, 128.6, 127.9, 127.5, 114.6, 80.4, 70.0, 66.2, 60.8, 38.5, 15.1, 14.2.

(f) (S)-2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester

3-(4-Benzyloxyphenyl)-2-(S)-ethoxypropanoic acid (7.13 g; 21.7 mmole) was hydrogenated at atmospheric pressure for 2 hours in ethyl acetate (70 ml) using Pd/C as catalyst. Purification by chromatography on silica gel using toluen:ethyl acetate as eluent

gave of 3.83 g (yield in 3 step 76 %) (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.18 (t, 3H, J=6.8 Hz), 1.24 (t, 3H, J=7 Hz), 2.96 (d, 2H, J=6.5 Hz), 3.34-3.43 (m, 1H), 3.57-3.66 (m, 1H), 4.00 (t, 1H, 6.5 Hz), 4.18 (q, 2H, J=7 Hz), 5.30 (s, 1 OH), 6.74 (dm, 2H, J=8.5 Hz, unresolved), 7.10 (dm, 2H, J=8.5 Hz, unresolved).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.2, 15.0, 38.4, 60.9, 66.2, 80.4, 115.1, 129.0, 130.5, 154.5, 172.7.

(g) (S)-2-Ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester.

Azodicarbonyl dipiperidine (0.99 g; 3.93 mmole) and triphenylphosphine (1.03 g; 3.93 mmole) were added to a solution of N-[4-(2-hydroxyethyl)phenyl]isobutyramide (0.79 g; 3.93 mmole) and (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester (0.78 g; 3.27 mmole) in dry dichloromethane (25 ml). After stirring at room temperature over night 0.65 mmole more of N-[4-(2-hydroxyethyl)phenyl]isobutyramide, azodicarbonyl dipiperidine and triphenylphosphine were added. After stirring for 24 hours the reaction mixture was filtered, the solvent was evaporated *in vacuo* and purification by chromatography on silica gel using heptan:ethyl acetate (2:1) as eluent gave 1.22 g (yield 87%) of (S)-2-ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 1.20-1.26 (m, 9H), 2.55 (qvint, 1H, J=6.7 Hz), 2.95-2.98 (m, 2H), 3.03 (t, 2H, J=7 Hz), 3.33-3.41 (m, 1H), 3.57-3.65 (m, 1H), 3.98-4.02 (m, 1H), 4.12 (t, 2H, J=7 Hz), 4.17 (q, 2H, J=7 Hz), 6.82 (dm, 2H, J=8.6 Hz, unresolved), 7.15 (dm, 2H, J=8.6 Hz, unresolved), 7.29 (dm, 2H, J=8.6 Hz, unresolved), 7.53 (dm, 2H, J=8.6 Hz, unresolved).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.0, 14.9, 19.4, 35.0, 36.1, 38.2, 60.6, 65.9, 68.4, 80.1, 114.1, 120.0, 129.0, 129.1, 130.1, 133.7, 136.6, 157.3, 172.4, 175.6.

Example 60. (S)-2-Ethoxy-3-[4-(2-{4-isobutyrylaminophenyl}ethoxy)phenyl]propanoic acid

(S)-2-Ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}-ethoxy)phenyl]propanoic acid in example 2 to give (S)-2-ethoxy-3-{4-[2-(4-methanesulfonylphenyl)ethoxy]phenyl}propanoic acid.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 1.70 (d, 6H, J=7.3 Hz), 2.45-2.57 (m, 1H), 2.91-2.98 (m, 1H), 3.01-3.10 (m, 1H), 3.39-3.48 (m, 1H), 3.56-3.65 (m, 1H), 4.01-4.06 (m, 1H), 4.12 (t, 2H, J=7 Hz), 6.80 (dm, 2H, J=8.8 Hz, unresolved), 7.14 (dm, 2H, J=8.8 Hz, unresolved), 7.22 (dm, 2H, J=8.3 Hz, unresolved), 7.31 (bs, 1NH), 7.47 (dm, 2H, J=8.3 Hz, unresolved).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 15.0, 19.6, 35.2, 36.6, 37.8, 66.7, 68.6, 79.8, 114.4, 120.0, 128.7, 129.4, 130.4, 134.1, 136.4, 157.7, 174.6, 175.3.

Example 61. (R)-2-Ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester

(a) 3-(4-Benzyloxyphenyl)-2-(R)-ethoxypropanoic acid

Concentrated sulfuric acid (3.9 ml) was slowly added to a solution of 3-(4-benzyloxyphenyl)-(R)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide (1.24 g; 2.96 mmole) in dioxane:water (1:1, 3.9 ml). The reaction mixture was stirred at 80° C for 5 hours, at room temperature for 14 hours, and then poured onto water (30 ml). The

crude product was extracted twice with ethyl acetate (30 ml), and dried (sodium sulfate) and purified by chromatography on silica gel using heptane:ethyl acetate:acetic acid (10:10:1) as eluent to give 0.67 g (yield 76 %) of 3-(4-benzyloxyphenyl)-2-(R)-ethoxypropanoic acid.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.16 (t, 3H, J=6.9 Hz), 2.94 (dd, 1H, J=7.8 and 7.8 Hz), 3.07 (dd, 1H, J=4.2 and 4.2 Hz), 3.42 (m, 1H), 3.60 (m, 1H), 4.04 (m, 1H), 5.03 (s, 2H), 6.90 (dm, 2H, J=8.6 Hz, unresolved), 7.16 (dm, 2H, J= 8.5 Hz, unresolved), 7.30-7.43 (m, 5H).

(b) 3-(4-Benzyloxyphenyl)-(R)-2-ethoxypropanoic acid ethyl ester

Oxalyl chloride (0.234 ml; 2.68 mmole) was slowly added to a solution of 3-(4-benzyloxyphenyl)-2-(R)-ethoxypropanoic acid (0.67 g; 2.23 mmole) in dichloromethane (10 ml). After stirring at room temperature for 1 hour, the reaction mixture was cooled on an ice bath and ethanol (0.5 ml) was added. After 3 hours ethanol (10 ml) was added and hydrogen chloride (g) bubbled through the solution. After 2 hours the solvent was evaporated *in vacuo*, and the crude product was purified by chromatography on silica gel using heptane:ethyl acetate (5:1) as eluent to give 0.58 g (yield 78 %) of 3-(4-benzyloxyphenyl)-(R)-2-ethoxypropanoic acid ethyl ester.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.12-1.24 (m, 6H), 2.94 (d, 2H, J=7.7 Hz), 3.34 (m, 1H), 3.59 (m, 1H), 3.96 (t, 1H), 4.15 (q, 2H, J=7.1 Hz), 5.03 (s, 2H), 6.88 (dm, 2H, J=8.7 Hz, unresolved), 7.15 (dm, 2H, J= 8.7 Hz, unresolved), 7.23-7.45 (m, 5H).

(c) (R)-2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester

3-(4-Benzyloxyphenyl)-(R)-2-ethoxypropanoic acid ethyl ester (0.58 g;1.75 mmole) was hydrogenated at atmospheric pressure in ethanol using Pd/C as catalyst to give 0.4 g (yield 95%) of (R)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.15 (t, 3H, J=7 Hz), 1.21 (t, 3H, J=7 Hz), 2.93 (d, 2H, J=6.6 Hz), 3.35 (m, 1H), 3.59 (m, 1H), 3.97 (t, 1H), 4.15 (q, 2H, J=7 Hz), 5.20 (s br, 1 OH), 6.72 (dm, 2H, J=8.5 Hz, unresolved), 7.08 (dm, 2H, J= 8.5 Hz, unresolved).

(d) (R)-2-Ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester

Azodicarbonyl dipiperidine (0.573 g; 2.27 mmole) and triphenylphosphine (0.595 g; 2.27 mmole) were added to a solution of N-[4-(2-hydroxyethyl)phenyl]isobutyramide (0.459 g; 2.27 mmole) and (R)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester (0.36 g; 1.51 mmole) in dry dichloromethane (20 ml). After stirring at room temperature over night the reaction mixture was filtered, solvent was evaporated *in vacuo* and purification by chromatography on silica gel using heptan:ethyl acetate (2:1) as eluent gave of (R)-2-ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester (0.52 g; yield 81%).

^{1}H NMR (600 MHz; $CDCl_3$): δ 7.48 (d, J=8.3 Hz, 2H), 7.24 (d, J=8.3 Hz, 2H), 7.19 (s, br, 1H), 7.15 (d, J=8.6 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 4.17 (q, J=7.1 Hz, 2H), 4.12 (t, J=7.1 Hz, 2H), 3.97 (dd, J=7.4 and 5.9 Hz, 1H), 3.60 (dq, J=9.1 and 7.0 Hz, 1H), 3.36 (dq, J=9.1 and 7.0 Hz, 1H), 3.05 (t, J=7.1 Hz, 2H), 2.95 (m, 2H), 2.51 (sept, J=6.9 Hz, 1H), 1.26 (d, J=6.9 Hz, 6H), 1.23 (t, J=7.1 Hz, 3H), 1.17 (t, J=7.0 Hz, 3H).

Example 62. (R)-2-Ethoxy-3-[4-(2-{4-isobutyrylaminophenyl}ethoxy)phenyl]propanoic acid

(R)-2-Ethoxy-3-{4-[2-(4-isobutyrylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester was hydrolyzed in the same way as in 2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl]propanoic acid in example 2 to give (R)-2-ethoxy-3-[4-(2-{4-isobutyrylaminophenyl}ethoxy)phenyl]propanoic acid.

^{1}H NMR (600 MHz; $CDCl_3$): δ 9.0 (s, br, 1H), 7.8 (s, br, 1H), 7.48 (d, J=8.1 Hz, 2H), 7.19 (d, J=8.1 Hz, 2H), 7.14 (d, J=8.1 Hz, 2H), 6.79 (d, J=8.1 Hz, 2H), 4.09 (t, J=6.8 Hz, 2H), 4.03 (m, 1H), 3.62 (m, 1H), 3.89 (m, 1H), 3.01 (t, J=6.8 Hz, 2H), 2.94 (m, 1H), 2.54 (m, 1H),1.21 (d, J=7.0 Hz, 6H), 1.15 (t, J=6.8 Hz, 3H).

^{13}C NMR (150 MHz; $CDCl_3$): δ 176.0, 175.8, 157.5, 136.3, 134.1, 130.3, 129.2, 128.9, 120.3, 114.3, 79.8, 68.5, 66.4, 37.9, 36.3, 35.1, 19.4, 14.9.

Example 63. 2-Ethoxy-3-(4-{2-[4-(isobutyryl-N-methylamino)phenyl]ethoxy}phenyl)-propanoic acid ethyl ester

2-Ethoxy-3-{4-[2-(4-methylaminophenyl)ethoxy]phenyl}propanoic acid ethyl ester (0.477 mg; 1.28 mmole) was dissolved in a solution of isobutyric anhydride (2 ml) and pyridine (4 ml) and the reaction mixture was stirred for 2 hours at room temperature. Toluene was added and evaporation *in vacuo* and purification by chromatography on silica gel using heptan:ethyl acetate (1:1) as eluent gave 0.44 g (yield 78 %) of 2-ethoxy-3-(4-{2-[4-(isobutyryl-N-methylamino)phenyl]ethoxy}phenyl)propanoic acid ethyl ester.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.33 (d, J=8.2 Hz, 2H), 7.15 (d, J=8.6 Hz, 2H), 7.12 (d, J=8.2 Hz, 2H), 6.82 (d, J=8.6 Hz, 2H), 4.17 (m, 4H), 3.97 (dd, J=7.1 and 6.1 Hz, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 3.23 (s, 3H), 3.11 (t, J=7.1 Hz, 2H), 2.95 (m, 2H), 2.52 (sept, J=6.7 Hz, 1H), 1.23 (t, J=7.1 Hz, 3H), 1.16 (t, J=6.9 Hz, 3H), 1.03 (d, J=6.7 Hz, 6H).

Example 64. 2-Ethoxy-3-(4-{2-[4-(isobutyryl-N-methylamino)phenyl]ethoxy}phenyl)-propanoic acid

Lithium hydroxide hydrate (62 mg; 1.48 mmole) dissolved in 2 ml water was added to a solution of 2-ethoxy-3-(4-{2-[4-(isobutyryl-N-methylamino)phenyl]ethoxy}phenyl)-propanoic acid ethyl ester (435 mg; 0.98 mmole) in tetrahydrofuran (6 ml). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was acidified with hydrochloric acid (2 M) to pH 4. Tetrahydrofuran was evaporated *in vacuo*, 5 ml

water was added and the product was extracted with ethyl acetate (10 ml), dried (sodium sulfate) and solvent was evaporated *in vacuo* to give 398 mg (yield 98 %) of 2-ethoxy-3-(4-{2-[4-(isobutyryl-N-methylamino)phenyl]ethoxy}phenyl)propanoic acid.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.02 (d, 6H, J=6.6 Hz), 1.16 (t, 3H, J=7 Hz), 2.49 (qvint, 1H, J=6.6 Hz), 2.84-3.15 (m, 4H), 3.22 (s, 3H), 3.29-3.46 (m, 1H), 3.52-3.69 (m, 1H), 3.94-4.06 (m, 1H), 4.17 (t, 2H, J=6.6 Hz), 6.82 (dm, 2H, J=8.4 Hz, unresolved), 7.05-7.22 (m, 4H). 7.33 (dm, 2H, J=8 Hz, unresolved).
^{13}C-NMR (75 MHz; $CDCl_3$): δ 15.1, 19.6, 31.0, 35.3, 37.6, 38.0, 66.6, 68.2, 79.8, 114.4, 127.2, 129.3, 130.4, 130.5, 138.3, 142.4, 157.5, 175.3, 178.0.

Biological activity

The biological activity of the compounds of the invention was tested in obese diabetic mice of the Umeå ob/ob strain. Groups of mice received the test compound by gavage once daily for 7 days. On the last day of the experiment the animals were anesthetized 2h after dose in a non-fed state and blood was collected from an incised artery. Plasma was analyzed for concentration of glucose, insulin and triglycerides. A group of untreated obese diabetic mice of the same age served as control. The weight of the mice was measured before and after the experiment and the obtained weight gain was compared to the weight gain of the control animals. The individual values for glucose, insulin and triglyceride levels of the mice from the test group were expressed as the percent rage of the corresponding values from the control group.

The desired "therapeutic effect" was calculated as the average percent reduction of the three variables glucose, insulin and triglycerides below the levels in the control animals. The therapeutic effect of the tested compounds according to the invention was compared to the same effect in the prior art compound troglitazone, administrered by gavage in the oral dose of 100 μmol/kg for 7 days.

The superior effects of the tested compounds according to the invention compared to that of troglitazone when given in the same oral dose demonstrate the increased potency and efficiacy of the claimed compounds.

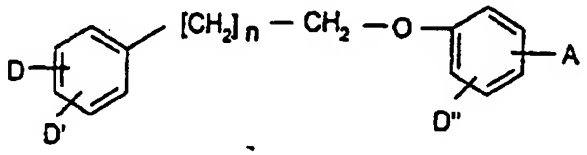
Abbreviations

NIDDM	non insulin dependent diabetes mellitus
IRS	insulin resistance syndrom
VLDL	very low density lipoproteins
HDL	high density lipoproteins
PPAR	peroxisome proliferator activated receptor
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilylamine
DMF	dimethylformamide
CH_3CN	acetonitrile
DEAD	diethyl azodicarboxylate
ADDP	azodicarbonyl dipiperidine
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
DCC	dicyclohexylcarbodiimide
HBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
TBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
PyBop	benzotriazole-1-yl-oxy-tris-pyrolidino-phosphonium hexafluorophosphate
DMAP	4-dimethylaminopyridine
HOBt	1-hydroxybenzotriazole
TEA	triethylamine
DiPEA	diisopropylethylamine
TLC	thin layer chromatography
THF	tetrahydrofuran
Pd/C	palladium on charcoal
H2O	1-hydroxybenzotriazole-hydrate

	t	triplet
	s	singlet
	d	doublet
	q	quartet
s	qvint	quintet
	m	multiplet
	br	broad

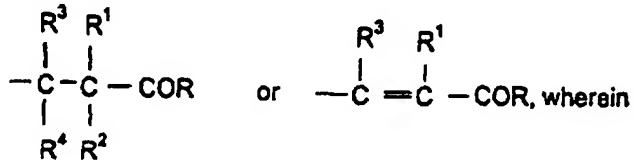
CLAIMS

1. A compound having the general formula



I

and stereo - and optical isomers and racemates thereof as well as pharmaceutically acceptable salts, solvates and hydrates thereof, in which formula A is situated in the orto, meta or para position and represents



R is -OR^a, wherein R^a represents hydrogen, alkyl, aryl or alkylaryl;
-NR^bR^a, wherein R^b and R^a are the same or different and R^b represents hydrogen, alkyl, aryl, alkylaryl, cyano, - OH, -Oalkyl, -Oaryl, -Oalkylaryl, -COR^c or -SO_2R^d, wherein R^c represents hydrogen, alkyl, aryl or alkylaryl and R^d represents alkyl, aryl or alkylaryl;

R^1 is alkyl, aryl, alkylaryl, alkene, alkyne, cyano,
-OR^e, wherein R^e is alkyl, acyl, aryl or alkylaryl;
-$[CH_2]_m$ -OR^f, wherein R^f represents hydrogen, alkyl, acyl, aryl or alkylaryl and m represents an integer 1-8;
-O-$[CH_2]_m$ -OR^f, wherein m and R^f are as defined above;
-OSO_2R^d, wherein R^d is as defined above;
-$OCONR^aR^c$, wherein R^a and R^c are as defined above;
-SR^d, wherein R^d is as defined above;

$-SO_2NR^aR^f$, wherein R^f and R^a are as defined above;

$-SO_2OR^a$, wherein R^a is as defined above;

$-SOR^d$, wherein R^d is as defined above;

$-SO_2R^d$, wherein R^d is as defined above;

$-NR^aR^g$, wherein R^a is as defined above and R^g represents hydrogen, alkyl, aryl, alkylaryl or $-SO_2R^d$, wherein R^d is as defined above;

$-NR^cCOR^a$, wherein R^c and R^a are as defined above;

$-NR^cCOOR^d$, wherein R^c and R^d are as defined above;

$-NR^fCONR^aR^c$, wherein R^f, R^a and R^c are as defined above;

$-COR^f$, wherein R^f is as defined above;

$-COOR^d$, wherein R^d is as defined above; or

$-CONR^cR^a$, wherein R^c and R^a are as defined above;

R^2 is hydrogen, alkyl, aryl, or alkylaryl,

R^3 and R^4 are the same or different and each represents hydrogen, alkyl, aryl, alkylaryl or $-OR^f$, wherein R^f is as defined above;

n is an integer 1-6,

D is situated in the orto, meta or para position and represents

$-OSO_2R^d$, wherein R^d is as defined above;

$-OCONR^fR^a$, wherein R^f and R^a are as defined above;

$-NR^cCOOR^d$, wherein R^c and R^d are as defined above;

$-NR^cCOR^a$, wherein R^c and R^a are as defined above;

$-NR^gR^a$, wherein R^g and R^a are as defined above, provided that R^g and R^a are not simultaneously hydrogen;

$-NR^fCONR^aR^c$, wherein R^c, R^a and R^f are as defined above;

$-SO_2R^d$, wherein R^d is as defined above;

$-SOR^d$, wherein R^d is as defined above;

$-SR^c$, wherein R^c is as defined above;

$-SO_2NR^aR^f$, wherein R^f and R^a are as defined above;

$-SO_2OR^a$, wherein R^a is as defined above;

-CN,

-$CONR^cR^a$, wherein R^c and R^a are as defined above;

D' is situated in the orto, meta or para position and represents

hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

D'' is situated in the orto, meta or para position and represents

hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$ wherein R^f and R^b are as defined above;

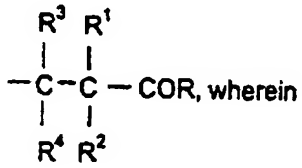
$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

with the exception of (R) - and (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl] propanoic acid.

2. A compound according to claim 1, wherein

A is situated in the meta or para position and represents,



R is $-OR^a$, wherein R^a is as defined above;

R^1 is alkyl, aryl, alkylaryl, alkene, alkyne, cyano,

$-OR^c$, wherein R^c is as defined above;

$-[CH_2]_m-OR^f$ wherein R^f and m are as defined above;

$-O-[CH_2]_m-OR^f$, wherein m and R^f are as defined above;

$-OCONR^aR^c$, wherein R^a and R^c are as defined above;

-SR^d, wherein R^d is as defined above;

-NR^aR^g, wherein R^a and R^g are as defined above;

-$COOR^d$, wherein R^d is as defined above;

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen, alkyl, aryl, alkylaryl or -OR^f, wherein R^f is as defined above;

n is an integer 1-3,

D is situated in the orto, meta or para position and represents

-OSO_2R^d, wherein R^d is as defined above;

-$OCONR^fR^a$ wherein R^f and R^a are as defined above;

-NR^cCOOR^d, wherein R^c and R^d are as defined above;

-NR^cCOR^a, wherein R^c and R^a are as defined above;

-NR^gR^a, wherein R^g and R^a are as defined above, provided that R^g and R^a are not simultaneously hydrogen;

-$NR^fCONR^aR^c$, wherein R^c, R^a and R^f are as defined above;

-SO_2R^d, wherein R^d is as defined above;

-SR^c, wherein R^c is as defined above;

-$CONR^cR^a$, wherein R^c and R^a are as defined above;

D' is situated in the orto, meta or para position and represents

hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, -NO_2, -NR^fR^b, wherein R^f and R^b are as defined above;

-OR^f, wherein R^f is as defined above;

-OSO_2R^d, wherein R^d is as defined above;

D'' is situated in the orto, meta or para position and represents

hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, -NO_2, -NR^fR^b, wherein R^f and R^b are as defined above;

-OR^f, wherein R^f is as defined above;

-OSO_2R^d, wherein R^d is as defined above.

3. A compound according to claim 2, wherein

A is situated in the para position,

R is $-OR^a$,

R^1 is - Oalkyl,

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen or alkyl,

n is an integer 1-3,

D is situated in the orto, meta or para position and represents $-NR^cCOOR^d$ or $-NR^cCOR^a$, wherein R^d, R^a and R^c are as defined above;

D' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

D'' is situated in the orto or meta position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above.

4. A compound according to claim 3, wherein

R is -OH, -Oalkyl or -Oalkylaryl,

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

n is the integer 2,

D is situated in the para position, and represents $-NHCOOR^d$ or $NHCOR^a$, wherein R^d and R^a are as defined above;

D' is hydrogen and

D'' is hydrogen.

5. A compound according to claim 2, wherein

A is situated in the para position,

R is $-OR^a$,

R^1 is -Oalkyl,

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen or alkyl,

n is an integer 1-3,

D is situated in the orto, meta or para position and represents
$-SO_2R^d$, wherein R^d is as defined above;

D' is situated in the orto, meta or para position and represents
hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;
$-OR^f$, wherein R^f is as defined above;
$-OSO_2R^d$, wherein R^d is as defined above;

D'' is situated in the orto or meta position and represents
hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;
$-OR^f$, wherein R^f is as defined above;
$-OSO_2R^d$, wherein R^d is as defined above.

6. A compound according to claim 5, wherein

R is -OH, -Oalkyl or -Oalkylaryl,

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

n is the integer 2,

D is situated in the para position.

D' is hydrogen and

D" is hydrogen.

7. A compound according to claim 2, wherein

A is situated in the para position,

R is $-OR^a$,

R^1 is -Oalkyl,

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen or alkyl,

n is an integer 1-3,

D is situated in the orto, meta or para position and represents

$-SR^c$, wherein R^c is as defined above;

D' is situated in the orto, meta or para position and represents

hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

D" is situated in the orto or meta position and represents

hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above.

8. A compound according to claim 7, wherein

R is -OH, -Oalkyl or -Oalkylaryl,

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

n is the integer 2,

D is situated in the para position,

D' is hydrogen and

D" is hydrogen.

9. A compound according to claim 2, wherein

A is situated in the para position,

R is $-OR^a$,

R^1 is -Oalkyl,

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen or alkyl,

n is an integer 1-3,

D is situated in the orto, meta or para position and represents $-OCONR^fR^a$, wherein R^f and R^a are as defined above;

D' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

D" is situated in the orto or meta position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above,

$-OSO_2R^d$, wherein R^d is as defined above.

10. A compound according to claim 9, wherein

R is -OH, -Oalkyl or -Oalkylaryl,

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

n is the integer 2,

D is situated in the para position, and represents
-OCONHR^d, wherein R^d is defined as above;
D' is hydrogen and
D" is hydrogen.

11. A compound according to claim 2, wherein
A is situated in the para position,
R is -OR^a,
R^1 is - Oalkyl,
R^2 is hydrogen or alkyl,
R^3 is hydrogen or alkyl,
R^4 is hydrogen or alkyl
n is an integer 1-3,
D is situated in the orto, meta or para position and represents
-NR^{a}SO$_2$R^d, wherein R^d and R^a are as defined above;
D' is situated in the orto, meta or para position and represents
hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, -NO$_2$, -NR^{f}R^b, wherein R^f and R^b are as defined above;
-OR^f, wherein R^f is as defined above;
-OSO$_2$R^d, wherein R^d is as defined above;
D" is situated in the orto or meta position and represents
hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, -NO$_2$, -NR^{f}R^b, wherein R^f and R^b are as defined above;
-OR^f, wherein R^f is as defined above,
-OSO$_2$R^d, wherein R^d is as defined above.

12. A compound according to claim 11, wherein
R is - -OH, -Oalkyl or -Oalkylaryl,
R^2 is hydrogen,
R^3 is hydrogen,

R^4 is hydrogen,

n is the integer 2,

D is situated in the para position, and represents $-NHSO_2R^d$ wherein R^d is as defined above;

D' is hydrogen and

D" is hydrogen.

13. A compound according to claim 2, wherein

A is situated in the meta or para position,

R is $-OR^a$,

R^1 is -Oalkyl,

R^2 is hydrogen or alkyl,

R^3 is hydrogen or alkyl,

R^4 is hydrogen or alkyl,

n is an integer 1-3,

D is situated in the orto, meta or para position and represents $-OSO_2R^d$, wherein R^d is defined as above;

D' is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, CN, NO_2, NR^fR^b, wherein R^f and R^b are as defined above,

$-OR^f$, wherein R^f is as defined above,

$-OSO_2R^d$, wherein R^d is as defined above.

D" is situated in the orto, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above,

$-OR^f$, wherein R^f is as defined above,

$-OSO_2R^d$, wherein R^d is as defined above.

14. A compound according to claim 13, wherein

A is situated in the para position,

R is -OH, -Oalkyl, -Oalkylaryl,

n is the integer 2,

D is situated in the para position.

15. A compound according to claim 14, wherein

R^2 is hydrogen,

R^3 is hydrogen,

R^4 is hydrogen,

D is $-OSO_2$ alkyl,

D' is hydrogen and

D'' is hydrogen.

16. A compound according to any of the preceding claims being

2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid,

3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid,

2-ethoxy-3-{4-[2-(4-methanesulfonylphenyl)ethoxy]phenyl}propanoic acid,

2-ethoxy-3-{4-[2-(4-methylsulfanylphenyl)ethoxy]phenyl}propanoic acid,

2-ethoxy-3-[4-(2-{4-isobutyrylaminophenyl}ethoxy)phenyl]propanoic acid,

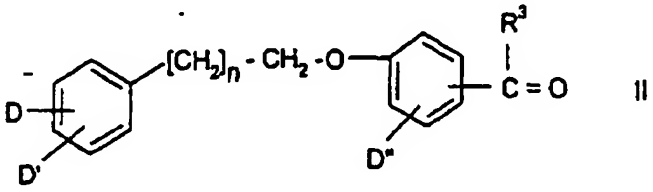
3-{4-[2-(4-*tert*-butylcarbamoyloxyphenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester or

2-ethoxy-3-{4-[2-(4-methanesulfonylaminophenyl)ethoxy]phenyl}propanoic acid.

17. A compound according to any of the preceding claims wherein the compound is one of the possible enantiomers.

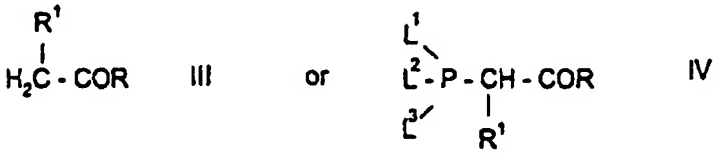
18. A process for preparing a compound according to claim 1, characterized by

a) condensating a compound of the formula II



II

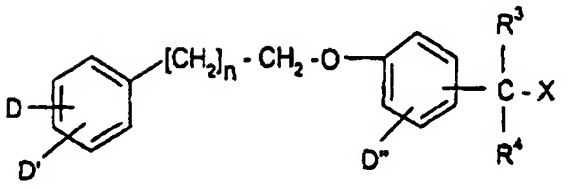
with a compound of the formula III or IV



III or IV

in which formulas D, D', D'', n, R, R^1 and R^3 are as defined in claim 1 and $L^1 = L^2 = L^3$ are phenyl or $L^1 = L^2$ are OR^d (wherein R^d is as defined in claim 1) and L^3 is =O, whereafter, if desired, reducing the double bond and removing protective groups, to the formation of a compound of formula I wherein R^2 and R^4 are hydrogen, or

b) reacting a compound of the formula VII



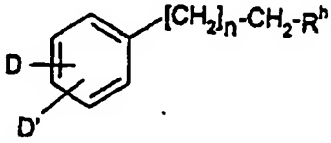
VII

with a compound of the formula VIII

VIII

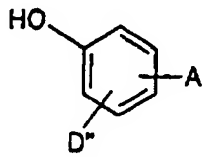
in which formulas D, D', D'', n, R, R^1, R^2, R^3 and R^4 are as defined in claim 1 and X is a leaving group, whereafter, if necessary, removing protective groups to the formation of a compound of the formula I wherein A is $-CR^3R^4-CR^1R^2-COR$, or

c) reacting a compound of the formula V



V

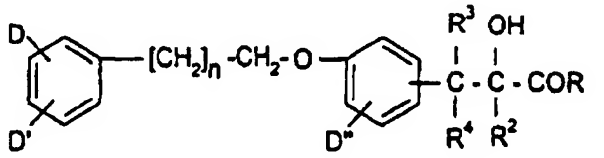
with a compound of the formula X



X

in which formulas D, D', D'', n and A are as defined in claim 1 and R^h is - OH or a leaving group, whereafter, if necessary, removing protective groups, or

d) converting a compound of the formula XI



XI

in which formula D, D', D'', n, R, R^2, R^3 and R^4 are as defined in claim 1, to the formation of a compound of the formula I wherein A is $-CR^3R^4-CR^1R^2-COR$, wherein R^1 is

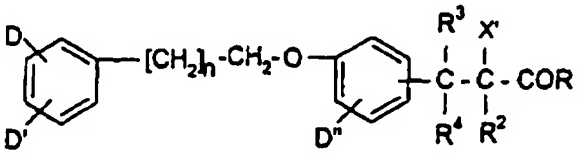
$-OR^e$ wherein R^e is as defined above,

$-O-[CH_2]_m-OR^f$ wherein m and R^f are as defined above,

$-OSO_2R^d$, wherein R^d is as defined above,

$-OCONR^aR^c$, wherein R^a and R^c are as defined above, or

e) reacting a compound of the formula XII



XII

with an amine, an alcohol or a thiol, in which formula D, D', D'', n, R, R^2, R^3 and R^4 are as defined in claim 1 and X' is halogen, to the formation of a compound of the formula I wherein A is $-CR^3R^4-CR^1R^2-COR$, wherein R^1 is

$-OR^d$, wherein R^d is as defined above,

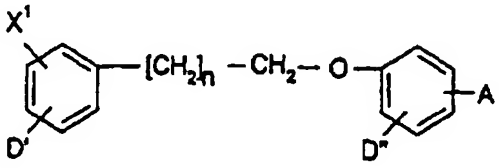
$-O-[CH_2]_m-OR^f$, wherein R^f is as defined above,

$-SR^d$, wherein R^d is as defined above,

$-NR^aR^g$, wherein R^a and R^g are as defined above,

$-NR^cCOR^d$, wherein R^c and R^d are as defined above; or

f) reacting a compound of the formula XIII



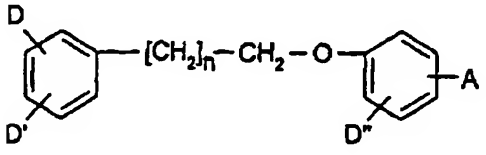
XIII

with a suitable reagent and followed by removal of protective groups, in which formula D', D'', n and A are as defined in claim 1 and X^1 is -OH, - SH or $-NH_2$ to the formation of a compound of the formula I wherein D is $-OSO_2R^d$, $-SR^c$, $-OCONR^fR^a$, $-NR^cCOOR^d$, $-NR^cCOR^a$, $-NR^gR^a$, $-NR^fCONR^aR^c$; wherein R^a, R^c, R^d, R^f and R^g are as defined above, or

g) hydrolysis of a compound of the formula I wherein R is OR^p, wherein R^p is a protective group, to the formation of a compound of the formula I wherein R is OH, or

h) reacting a compound of the formula I wherein R is OH with a compound of the formula HNR^bR^a, wherein R^b and R^a are as defined in claim 1, to the formation of a compound of the formula I wherein R is $-NR^bR^a$, or

i) oxidizing a compound of the formula XIV



XIV

and if necessary followed by removal of protective groups, in which formula D', D'', n and A are as defined in claim 1 and D is SOR^d or SR^d, to the formation of a compound of the formula I wherein D is $-SO_2R^d$ or $-SOR^d$; whereafter, if desired, the compound obtained according to any of methods a) - i) is converted to a stereoisomer, a pharmaceutically acceptable salt thereof, a solvate and/or a hydrate thereof.

19. A process according to claim 18, characterized by the preparation of a compound according to any of claims 2-17.

20. A compound according to any of claims 1-17 for use in therapy.

21. A pharmaceutical formulation containing a compound according to any of claims 1-17 as active ingredient optionally together with an acceptable carrier.

22. The use of a compound according to any of claims 1-17 in the manufacture of a formulation for the treatment of clinical conditions associated with insulin resistance.

23. A method for the treatment of clinical conditions associated with insulin resistance wherein a therapeutically active amount of a compound according to any of claims 1-17 administered to a mammal in the need of such treatment.

24. A pharmaceutical formulation for use in the treatment of clinical conditions associated with insulin resistance wherein the active ingredient is a compound according to any of claims 1-17.

Abstract

Novel 3-aryl propionic acid derivatives and analogs, process and intermediate for their manufacture, pharmaceutical preparations containing them and the use of the compounds in clinical conditions associated with insulin resistance.